

Full Paper

## Synthesis and Biological Activity of Some New Pyrazoline and Pyrrolo[3,4-c]pyrazole-4,6-dione Derivatives: Reaction of Nitrilimines with Some Dipolarophiles

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**Abstract:** Several 1,3-diaryl-5-(cyano-, aminocarbonyl- and ethoxycarbonyl)-2-pyrazoline, pyrrolo[3,4-c]pyrazole-4,6-dione and 1,3,4,5-tetraaryl-2-pyrazoline derivatives were prepared by the reaction of nitrilimine with different dipolarophilic reagents. The new compounds were characterized using IR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR and mass spectra. Biological screening of some compounds is reported.

**Keywords:** Pyrazoline, pyrrolo[3,4-c]pyrazole-4,6-dione, nitrilimine, dipolarophile, biological activity.

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### Introduction

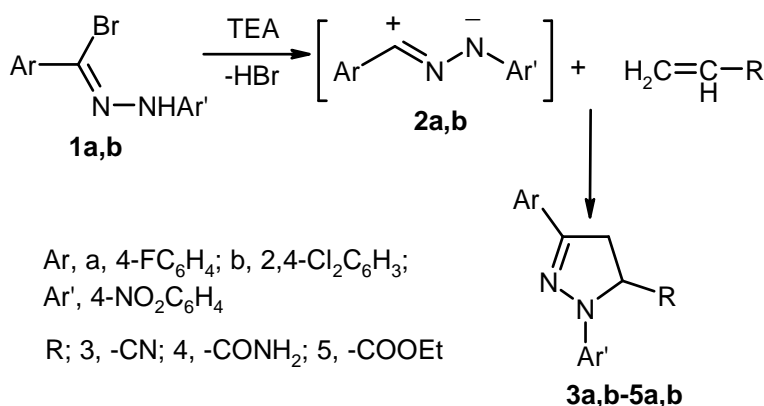
Considerable attention has been focused on pyrazolines and substituted pyrazolines due to their interesting biological activities. They have found to possess antifungal [1], antidepressant [2-5] anticonvulsant [4,5], anti-inflammatory [6], antibacterial [7] and anti-tumor [8] properties. Moreover,

many selectively fluoro-substituted organic compounds show peculiar pharmacological and agro-chemical properties [9-14]. Several methods are employed in the synthesis of pyrazolines, including the condensation of chalcones with hydrazine, hydrazine derivatives [15-19] and thiosemicarbazide [20] under acidic [15,16] or basic [20] conditions, and the cycloaddition of nitrilimines, generated *in situ* from the corresponding hydrazoneyl halides by the action of a suitable base, to carbon-carbon double bonds of a suitable dipolarophile [21-24]. As a connection of our interest in the preparation of heterocyclic compounds from hydrazoneyl halides [21-27] and the above-mentioned findings, the work reported herein was aimed at the preparation of some new pyrazoline derivatives with anticipated biological activities.

## Results and Discussion

The reactivity of the nitrilimines **2a,b**, generated *in situ* by base catalyzed elimination of hydrogen bromide from hydrazoneyl bromides **1a,b**, with various mono-, di- and tri-substituted dipolarophiles was examined. Thus, heating of equimolar amounts of **1a,b** and each of acrylonitrile, acrylamide or ethyl acrylate in dry benzene in the presence of triethylamine gave exclusively 3-aryl-1-(4-nitrophenyl)-5-substituted-2-pyrazolines **3a,b-5a,b**, respectively, in good yields (Scheme 1).

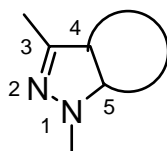
Scheme 1.



The assigned 5-substituted-2-pyrazoline structures **3-5** were supported by elemental analyses and spectroscopic data (see Experimental). The chemical shifts of the methine and methylene hydrogens in the <sup>1</sup>H-NMR spectra of **3-5** compared favorably with those reported for the corresponding protons in 1-aryl-3-(2-naphthoyl)-5-substituted-2-pyrazolines [21]. Such similarity, while confirming the assigned structures, indicates that both substituents, the 4-fluorophenyl- and 2,4-dichlorophenyl-, have similar effects on the chemical shifts of the methylene protons at C-4 of substituted 2-pyrazoline derivatives, compared with the 2-naphthoyl- group. The structures of **3a,b** were also confirmed by the absence of the nitrile absorption in the IR spectra, as observed in the case of aliphatic nitriles activated by a nitrogen or an oxygen atom in the β-position [28,29]. The IR spectra of **4a,b** showed the C=O amide absorption band at  $\nu$  1680 cm<sup>-1</sup> and NH<sub>2</sub> absorption bands at  $\nu$  3420 and 3300 cm<sup>-1</sup>. The IR of **5a,b** exhibited an ester carbonyl absorption band near  $\nu$  1730 cm<sup>-1</sup>. The <sup>13</sup>C-NMR spectrum of **5b** displays the characteristic signals of the suggested structure. The signal for the carbonyl carbon of

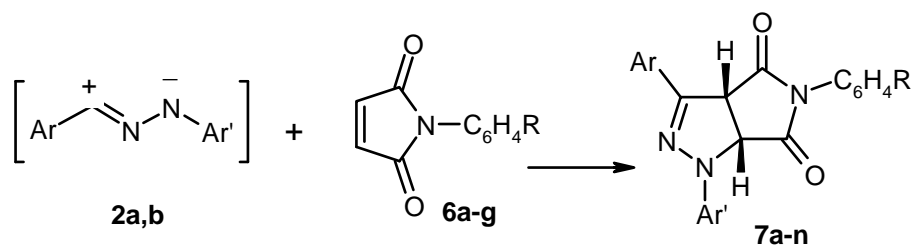
ester group appears at  $\delta$  169.4 ppm, the signals for pyrazoline C-4 at  $\delta$  39.9, pyrazoline C-5 at  $\delta$  59.9, the ester group methylene carbon at  $\delta$  61.6 and ester group methyl carbon at  $\delta$  13.8 ppm (see Figure 1 for the carbon numbering).

Figure 1.



Treatment of each of the hydrazoneyl bromides **1a** and **1b** with N-arylmaleimides **6a-g** in refluxing chloroform in the presence of triethylamine gave the corresponding cycloadducts **7a-n**, respectively (Scheme 2).

Scheme 2.



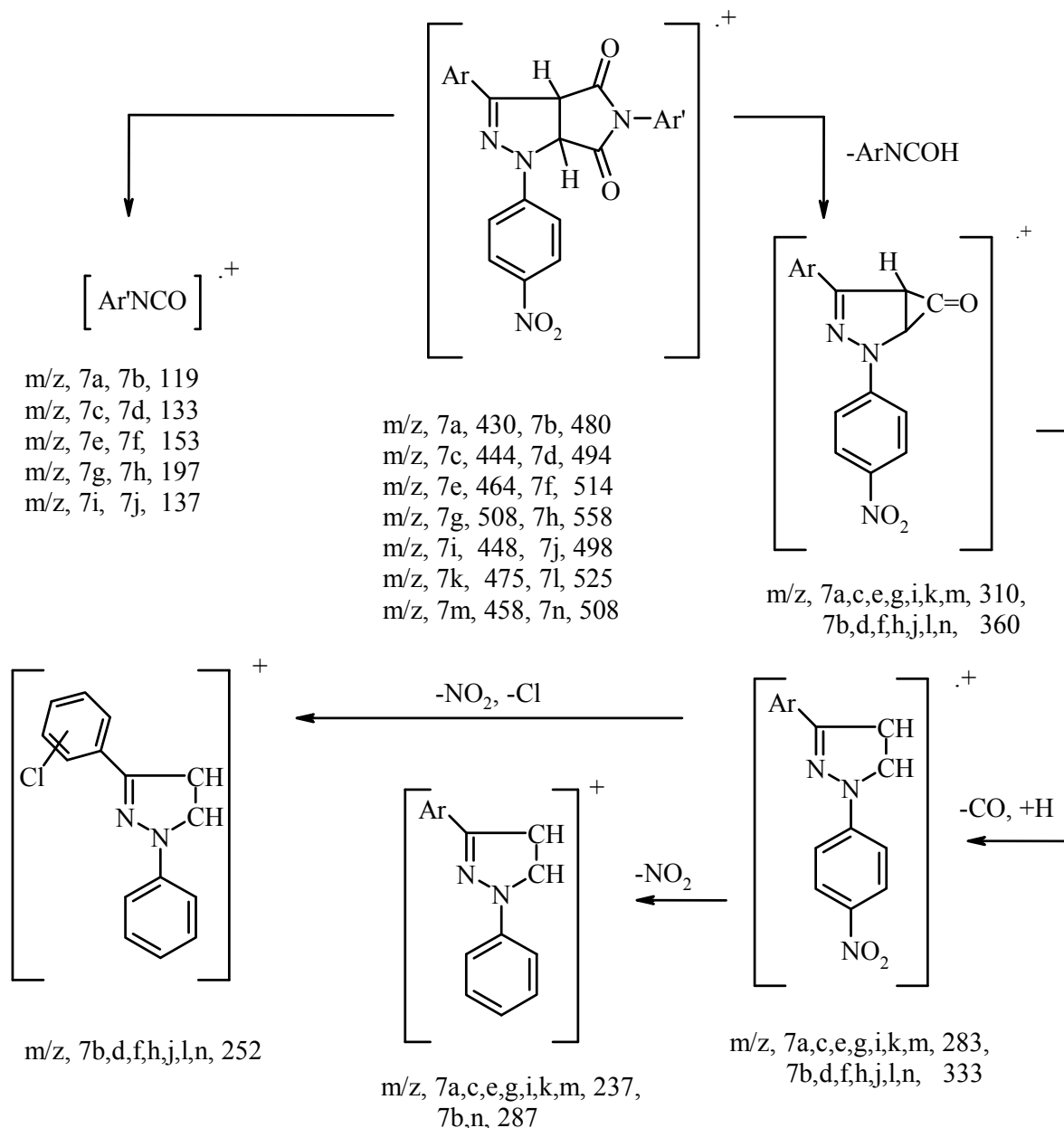
	Ar \ R		Ar \ R		Ar \ R
7a	a \ H	7f	b \ p-F	7k	a \ p-NO <sub>2</sub>
7b	b \ H	7g	a \ p-Cl	7l	b \ p-NO <sub>2</sub>
7c	a \ p-CH <sub>3</sub>	7h	b \ p-Cl	7m	a \ p-C <sub>2</sub> H <sub>5</sub>
7d	b \ p-CH <sub>3</sub>	7i	a \ p-Br	7n	b \ p-C <sub>2</sub> H <sub>5</sub>
7e	a \ p-F	7j	b \ p-Br		

Ar = a, 4-FC<sub>6</sub>H<sub>4</sub>; b, 2,4-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>; Ar' = 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>

The structure of the latter products was elucidated on the basis of their elemental analyses and the study of their spectroscopic data (see Experimental). The IR spectra of products **7** exhibit characteristic bands near  $\nu$  1720 cm<sup>-1</sup>, assignable to a carbonyl group. The <sup>1</sup>H-NMR spectra of all compounds showed, in each case, two doublets near  $\delta$  5.5 and 5.8 ppm, assignable to the protons at C-3a and C-6a, respectively. The vicinal coupling constants have been shown to be diagnostic,  $J_{trans} < (6 \text{ Hz})$ ,  $J_{cis}$  (9-12 Hz) [30,31], so the observed values of the coupling constants ( $J = 10.0$ -11.5 Hz) are compatible with the expected *cis*-configuration. On the basis of these spectroscopic data, the products **7a-n** were assigned 3a,4,6,6a-tetrahydro-3,5-diaryl-1-(4-nitrophenyl)-1H,5H-pyrrolo[3,4-c]pyrazole-4,6-dione structures. The <sup>13</sup>C-NMR spectrum of **7m** exhibited two signals at  $\delta$  171.49 and 170.59 for the two amide carbonyl carbons. The signals at  $\delta$  66.54, 53.81, 27.33 and 14.78 are assignable to C-5 pyrazoline, C-4 pyrazoline (Figure 1) and the methylene and methyl carbons of the ethyl group respectively. The mass spectra of all prepared compounds **7a-n** displayed the correct molecular ion

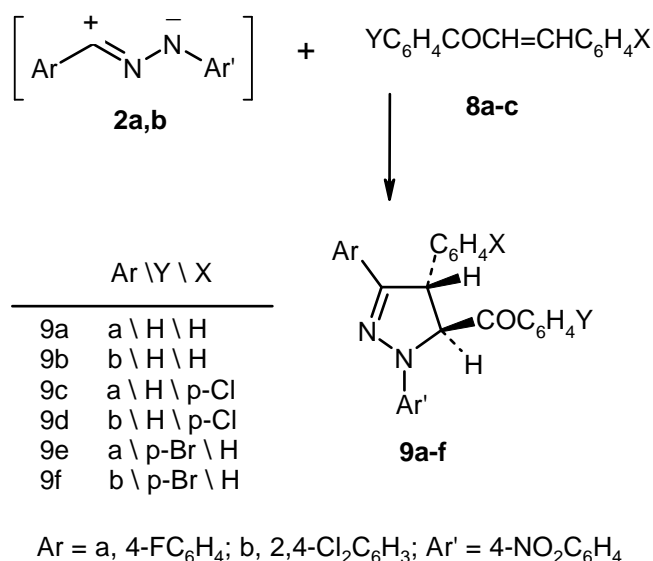
peaks. All molecular ion fragments seem to go through similar fragmentation pattern since the products with Ar = 4-FC<sub>6</sub>H<sub>4</sub> show the same fragment signals at M<sup>+</sup>, 310, 283, 237 and the products with Ar = 2,4-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub> show the same fragments at M<sup>+</sup>, 360, 333, 352. The fragmentation pattern of compounds **7** are shown in Scheme 3.

Scheme 3.



Also, treatment of the hydrazonoyl bromides **1a,b** with the appropriate  $\alpha,\beta$ -unsaturated ketones **8a-c** in benzene in the presence of triethylamine afforded, in each case, one regioisomer, as evidenced by TLC analysis. The structures of the products obtained were identified as **9a-f** respectively (Scheme 4). The structures of compounds **9** were assigned on the basis of their elemental analyses and spectroscopic data (see Experimental). The <sup>1</sup>H-NMR spectra of **9** were characterized, in each case, by the presence of two doublets ( $J = 3.6$ - $6.0$  Hz) near  $\delta$  5.2 and 6.5 ppm, assignable to the protons at C-4 and C-5 of the pyrazoline ring respectively [32].

## Scheme 4



On the basis of the coupling constant values [30,31], the cycloadducts **9** were assigned the *trans*-configuration. The <sup>13</sup>C-NMR spectra of compounds **9b** and **9f** revealed characteristic signals at δ 192.32 (191.71), 150.30 (150.29), 70.71 (70.63) and 56.54 (56.29) ppm, assignable to C=O, C=N, C-5 pyrazoline and C-4 pyrazoline, respectively. Also, the mass spectra of compounds **9** displayed molecular ion peaks in accordance with the suggested structures. The base peaks occur from elimination of benzoyl or bromobenzoyl at M<sup>+</sup>-105 or M<sup>+</sup>-183 respectively. Consequent loss of NO<sub>2</sub> gives fragments at M<sup>+</sup>-(105+46) or M<sup>+</sup>-(183+46), respectively. Other characteristic fragments resulting from cleavage β- to the carbonyl group also appeared at 105 or 183.

## Antimicrobial activity

Four of the newly synthesized compounds were screened for their antibacterial activity against the Gram -ve bacteria *Escherchia coli* and the Gram +ve bacteria *Staphylococcus aureus*, in addition to their antifungal activity against *Asperagillus flavus* and *Candida albicans* using the agar diffusion method [33,34] at a concentration 20 mg/mL using DMSO as a solvent. The results, recorded as average diameter of inhibition zone in mm, are given in Table I.

**Table 1.** Antimicrobial screening results of the tested compounds\*.

Comp. No.	<i>E. coli</i>	<i>S. aureus</i>	<i>A. flavus</i>	<i>C. albicans</i>
<b>3a</b>	11	11	0.0	11
<b>7i</b>	11	11	0.0	10
<b>7n</b>	11	11	0.0	10
<b>9c</b>	12	12	0.0	10
Tetracycline	32	34	--	--
Flucoral	--	--	14	16
Amphotricine	--	--	16	20

\* Zone of inhibition in mm

## Experimental

### General

All melting points were measured on an Electrothermal melting point apparatus and are uncorrected. The infrared spectra were recorded in potassium bromide disks on a Pye Unicam SP 3-300 or a Shimadzu FT-IR 8101 PC infrared spectrophotometer. The  $^1\text{H-NMR}$  (200 MHz) and  $^{13}\text{C-NMR}$  (50 MHz) spectra were recorded in DMSO- $d_6$  on a Varian Mercury VX 200 NMR using TMS as the internal reference. Mass spectra were measured on a GCMS-QP 1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Centre of Cairo University, Giza, Egypt. Compounds **1a** [35] and **1b** [36] were prepared according to the methods reported in the literature.

### Synthesis of 1,3,5-trisubstituted-2-pyrazoline derivatives **3a,b-5a,b**

To a solution of hydrazonoyl bromides **1a,b** (0.005 mol) and the appropriate monosubstituted olefin (acrylonitrile, acrylamide and ethyl acrylate, 0.005 mol) in chloroform (50 mL) was added triethylamine (0.7 mL, 0.005 mol) at room temperature. The mixture was refluxed for 4-6 h and then cooled. The mixture was extracted with water and the organic layer was collected, dried (anhydrous sodium sulfate) and then filtered. The solvent was evaporated and the residue was triturated with methanol whereupon it solidified. The solid was collected and recrystallized from the indicated solvents to give the corresponding cycloadducts **3-5** in good yield.

**5-Cyano-3-(4-fluorophenyl)-1-(4-nitrophenyl)-2-pyrazoline (3a)**. Yellowish brown solid; mp. 222-4 °C (from acetic acid); yield 73 %; IR:  $\nu/\text{cm}^{-1}$  3083.3 (CH-aromatic), 1596.5 (C=N); MS,  $m/z$ : 310 ( $M^+$ , 60.4), 284 (50.8), 283 (100.0), 236 (17.4), 133 (12.4), 95 (21.6), 90 (27.1), 75 (25.7), 63 (33.2), 50 (25.1);  $^1\text{H-NMR}$ :  $\delta/\text{ppm}$  3.79-3.94 (dd, 1H,  $J = 18.0, 12.0$  Hz), 3.96-4.07 (dd, 1H,  $J = 18.0, 6.0$  Hz), 5.86-5.94 (dd, 1H,  $J = 12.0, 6.0$  Hz), 7.29-8.27 (m, 8H, ArH's); Anal. Calcd. for  $\text{C}_{16}\text{H}_{11}\text{FN}_4\text{O}_2$ : C, 61.93; H, 3.57; N, 18.05; Found: C, 61.81; H, 3.63; N, 17.97.

**5-Cyano-3-(2,4-dichlorophenyl)-1-(4-nitrophenyl)-2-pyrazoline (3b)**. Yellow solid; mp. 164-6 °C (from dioxane-ethanol); yield 63 %; IR:  $\nu/\text{cm}^{-1}$  3091.3 (CH-aromatic), 1595.8 (C=N); MS,  $m/z$ : 362 ( $m^++2$ , 27.8), 360 ( $M^+$ , 45.3), 333 (78.5), 335 (37.9), 287 (14.7), 252 (23.3), 190 (10.0), 171 (18.1), 136 (20.7), 116 (32.5), 90 (63.8), 75 (59.9), 63 (100.0), 50 (74.6);  $^1\text{H-NMR}$ :  $\delta/\text{ppm}$  4.03 (d, 2H,  $J = 8.0$  Hz), 5.94 (t, 1H,  $J = 8.0$  Hz), 7.38-8.33 (m, 7 H, ArH's); Anal. Calcd. for  $\text{C}_{16}\text{H}_{10}\text{Cl}_2\text{N}_4\text{O}_2$ : C, 53.20; H, 2.79; N, 15.51; Cl, 19.63; Found: C, 53.15; H, 2.87; N, 15.42; Cl, 19.60.

**5-Aminocarbonyl-3-(4-fluorophenyl)-1-(4-nitrophenyl)-2-pyrazoline (4a)**. Orange yellow solid; mp. 301-3 °C (from dioxane); yield 54 %; IR:  $\nu/\text{cm}^{-1}$  3423.6, 3304.8 ( $\text{NH}_2$ ), 3185.3, 3078.3 (CH-aromatic), 1683.4 (C=O amide), 1598.2 (C=N); MS,  $m/z$ : 328 ( $M^+$ , 11.3), 284 (100.0), 238 (56.6), 90 (12.9), 76 (16.3), 50 (14.9);  $^1\text{H-NMR}$ :  $\delta/\text{ppm}$  3.44-3.58 (dd, 1H,  $J = 17.4, 6.0$  Hz), 3.76-3.91 (dd, 1H,  $J = 17.4, 12.4$  Hz), 4.93-5.02 (dd, 1H,  $J = 12.4, 6.0$  Hz), 7.06-8.19 (m, 10 H, ArH's,  $\text{NH}_2$ ); Anal. Calcd. for  $\text{C}_{16}\text{H}_{13}\text{FN}_4\text{O}_3$ : C, 58.53; H, 3.99; N, 17.06; Found: C, 58.56; H, 3.87; N, 16.89.

*5-Aminocarbonyl-3-(2,4-dichlorophenyl)-1-(4-nitrophenyl)-2-pyrazoline (4b)*. Orange yellow solid; mp. 257-9 °C (from dioxane); yield 53 %; IR:  $\nu/cm^{-1}$  3420.5, 3313.9 (NH<sub>2</sub>), 3074.8 (CH-aromatic), 1683.8 (C=O amide), 1595.1 (C=N); MS, m/z: 380 (M<sup>+</sup>+2, 7.2), 378 (M<sup>+</sup>, 9.8), 336 (67.5), 334 (100.0), 290 (29.5), 288 (48.1), 90 (11.8), 76 (12.8), 63 (10.3), 50 (10.6); <sup>1</sup>H-NMR:  $\delta/ppm$  3.44-3.57 (dd, 1H, *J* = 6.6, 18.4 Hz), 3.88-4.03 (dd, 1H, *J* = 18.4, 12.6 Hz), 4.94-5.04 (dd, 1H, *J* = 12.6, 6.6 Hz), 7.07-8.21 (m, 9H, ArH's, NH<sub>2</sub>); Anal. Calcd. for C<sub>16</sub>H<sub>12</sub>N<sub>4</sub>O<sub>3</sub>Cl<sub>2</sub>: C, 50.67; H, 3.18; N, 14.77; Cl, 18.69; Found: C, 50.66; H, 3.20; N, 14.78; Cl, 18.69.

*5-Ethoxycarbonyl-3-(4-fluorophenyl)-1-(4-nitrophenyl)-2-pyrazoline (5a)*. Yellow solid; mp. 184-6 °C (from benzene); yield 58 %; IR:  $\nu/cm^{-1}$  3071.9 (CH-aromatic), 2977.1, 2935.3 (CH-aliphatic), 1733.2 (C=O ester), 1593.4 (C=N); MS, m/z: 357 (M<sup>+</sup>, 18.7), 284 (100.0), 238 (57.4), 90 (10.2), 75 (12.6), 50 (7.4); <sup>1</sup>H-NMR:  $\delta/ppm$  1.21 (t, 3H, *J* = 7.4 Hz, COOCH<sub>2</sub>CH<sub>3</sub>), 3.60-3.71 (dd, 1H, *J* = 18.2, 5.0 Hz), 3.82-3.97 (dd, 1H, *J* = 18.2, 12.4 Hz), 4.13-4.24 (q, 2H, *J* = 7.4 Hz, COOCH<sub>2</sub>CH<sub>3</sub>), 5.32-5.41 (dd, 1H, *J* = 12.4, 5.0 Hz), 7.12-8.20 (m, 8H, ArH's); Anal. Calcd. for C<sub>18</sub>H<sub>16</sub>FN<sub>3</sub>O<sub>4</sub>: C, 60.49; H, 4.51; N, 11.75; Found: C, 60.52; H, 4.41; N, 11.64.

*5-Ethoxycarbonyl-3-(2,4-dichlorophenyl)-1-(4-nitrophenyl)-2-pyrazoline (5b)*. Orange yellow solid; mp. 130-2 °C (from acetic acid); yield 74 %; IR:  $\nu/cm^{-1}$  3074.9 (CH-aromatic), 2997.8, 2980.4 (CH-aliphatic), 1728.8 (C=O ester), 1594.8 (C=N); MS, m/z: 409 (M<sup>+</sup>+2, 10.8), 407 (M<sup>+</sup>, 16.2), 335 (100.0), 334 (92.9), 289 (45.7), 288 (50.9), 117 (10.7), 90 (23.9), 76 (25.2), 63 (22.2), 50 (20.1); <sup>1</sup>H-NMR:  $\delta/ppm$  1.21 (t, 3H, *J* = 7.1 Hz, COOCH<sub>2</sub>CH<sub>3</sub>), 3.67-3.78 (dd, 1H, *J* = 18.0, 4.6 Hz), 3.94-4.09 (dd, 1H, *J* = 18.0, 12.8 Hz), 4.17-4.24 (q, 2H, *J* = 7.1 Hz, COOCH<sub>2</sub>CH<sub>3</sub>), 5.35-5.44 (dd, 1H, *J* = 12.8, 4.6 Hz), 7.14-8.21 (m, 7H, ArH's); <sup>13</sup>C-NMR:  $\delta/ppm$  169.48 (C=O), 149.76, 148.34 (C=N, C-NO<sub>2</sub>), 139.01, 134.60, 132.35, 131.85 (4C, ArC's), 130.47, 128.40, 127.63, 125.75, 112.28 (5C, ArCH's), 61.67 (CH<sub>2</sub>, ester), 59.93 (C-5, pyrazoline), 39.95 (C-4, pyrazoline), 13.86 (CH<sub>3</sub>); Anal. Calcd. for C<sub>18</sub>H<sub>15</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>4</sub>: C, 52.95; H, 3.70; N, 10.29; Cl, 17.36; Found: C, 52.93; H, 3.62; N, 10.18; Cl, 17.29.

#### Synthesis of 3,5-diaryl-1-(4-nitrophenyl)-3a,4,6,6a-tetrahydro-1H,5H-pyrrolo[3,4-c]pyrazole-4,6-dione derivatives **7a-n**

Triethylamine (0.7 mL, 0.005 mol) was added to a solution of hydrazoneyl bromides **1a,b** (0.005 mol) and the *N*-arylmaleimides **6a-g** (0.005 mol) in benzene (50 mL). The mixture was refluxed for 2 h. The solid product was filtered off and washed with boiling ethanol (10 mL), then recrystallized from the indicated solvents to give **7a-n**.

*3-(4-Fluorophenyl)-1-(4-nitrophenyl)-5-phenyl-3a,4,6,6a-tetrahydro-1H,5H-pyrrolo[3,4-c]pyrazole-4,6-dione (7a)*. Yellow crystals; mp. 278-80 °C (from dimethylformamide); yield 91 %; IR:  $\nu/cm^{-1}$  3065.3 (CH-aromatic), 1721.0 (C=O), 1595.3 (C=N); MS, m/z: 430 (M<sup>+</sup>, 100.0), 310 (20.2), 283 (54.1), 237 (19.3), 237 (19.3), 119 (23.5), 91 (24.1), 63 (22.9), 50 (12.4); <sup>1</sup>H-NMR:  $\delta/ppm$  5.46 (d, 1H, *J* = 10.3 Hz), 5.83 (d, 1H, *J* = 10.3 Hz), 7.20-8.28 (m, 13H, ArH's); Anal. Calcd. for C<sub>23</sub>H<sub>15</sub>FN<sub>4</sub>O<sub>4</sub>: C, 64.18; H, 3.51; N, 13.01; Found: C, 63.99; H, 3.48; N, 12.98.

*3-(2,4-Dichlorophenyl)-1-(4-nitrophenyl)-5-phenyl-3a,4,6,6a-tetrahydro-1H,5H-pyrrolo[3,4-c]-pyrazole-4,6-dione (7b)*. Yellow crystals; mp. 206-7 °C (from toluene-ethanol); yield 94 %; IR:  $\nu/cm^{-1}$  3072.0 (CH-aromatic), 1719.2 (C=O), 1594.8 (C=N); MS, m/z: 484 ( $M^+ + 4$ , 16.8), 482 ( $M^+ + 2$ , 68.6), 480 ( $M^+$ , 100.0), 364 (5.2), 362 (20.6), 360 (33.0), 337 (13.6), 335 (60.9), 333 (74.8), 287 (15.1), 252 (29.9), 216 (13.2), 173 (14.9), 119 (49.8), 90 (79.4), 91 (68.2), 76 (51.0), 75 (48.0), 64 (65.6), 63 (89.6), 51 (33.7), 50 (42.2);  $^1H$ -NMR:  $\delta/ppm$  5.52 (d, 1H,  $J = 10.2$  Hz), 5.86 (d, 1H,  $J = 10.2$  Hz), 7.15-8.28 (m, 12H, ArH's); Anal. Calcd. for  $C_{23}H_{14}Cl_2N_4O_4$ : C, 57.39; H, 2.93; N, 11.64; Cl, 14.73; Found: C, 57.48; H, 3.02; N, 11.71; Cl, 14.71.

*3-(4-Fluorophenyl)-1-(4-nitrophenyl)-5-(4-methylphenyl)-3a,4,6,6a-tetrahydro-1H,5H-pyrrolo[3,4-c]pyrazole-4,6-dione (7c)*. Yellow crystals; mp. 304-6 °C (from dimethylformamide); yield 92 %; IR:  $\nu/cm^{-1}$  3066.2 (CH-aromatic), 2952.9 (CH-aliphatic), 1718.8 (C=O), 1595.2 (C=N); MS, m/z: 444 ( $M^+$ , 100.0), 310 (16.5), 283 (62.3), 237 (14.1), 133 (29.7), 117 (14.0), 104 (17.7), 90 (18.9), 63 (17.7), 50 (12.2);  $^1H$ -NMR:  $\delta/ppm$  2.33 (s, 3H,  $CH_3$ ), 5.44 (d, 1H,  $J = 10.9$  Hz), 5.81 (d, 1H,  $J = 10.9$  Hz), 7.18-8.28 (m, 12H, ArH's); Anal. Calcd. for  $C_{24}H_{17}FN_4O_4$ : C, 64.86; H, 3.85; N, 12.60; Found: C, 64.65; H, 3.79; N, 12.57.

*3-(2,4-Dichlorophenyl)-1-(4-nitrophenyl)-5-(4-methylphenyl)-3a,4,6,6a-tetrahydro-1H,5H-pyrrolo[3,4-c]pyrazole-4,6-dione (7d)*. Yellow crystals; mp. 275-7 °C (from dimethylformamide); yield 91 %; IR:  $\nu/cm^{-1}$  3089.4 (CH-aromatic), 2952.4 (CH-aliphatic), 1720.1 (C=O), 1593.8 (C=N); MS, m/z: 498 ( $M^+ + 4$ , 16.6), 496 ( $M^+ + 2$ , 63.5), 494 ( $M^+$ , 100.0), 335 (51.6), 333 (71.0), 252 (20.4), 133 (86.3), 132 (63.5), 117 (36.2), 116 (37.3), 105 (27.8), 104 (52.4), 91 (36.6), 90 (53.6), 89 (33.5), 78 (37.6), 77 (47.0), 76 (39.9), 75 (29.7), 63 (61.2), 51 (31.6), 50 (35.2);  $^1H$ -NMR:  $\delta/ppm$  2.34 (s, 3H,  $CH_3$ ), 5.55 (d, 1H,  $J = 10.8$  Hz), 5.86 (d, 1H,  $J = 10.8$  Hz), 7.15-8.29 (m, 11H, ArH's); Anal. Calcd. for  $C_{24}H_{16}Cl_2N_4O_4$ : C, 58.19; H, 3.25; N, 11.31; Cl, 14.31; Found: C, 58.19; H, 3.34; N, 11.32; Cl, 14.28.

*5-(4-Chlorophenyl)-3-(4-fluorophenyl)-1-(4-nitrophenyl)-3a,4,6,6a-tetrahydro-1H,5H-pyrrolo[3,4-c]pyrazole-4,6-dione (7e)*. Dark yellow crystals; mp. 298-300 °C (from dimethylformamide); yield 94 %; IR:  $\nu/cm^{-1}$  3064.7 (CH-aromatic), 1721.4 (C=O), 1595.1 (C=N); MS, m/z: 464 ( $M^+$ , 92.1), 310 (25.0), 283 (100.0), 237 (20.4), 153 (26.8), 90 (38.1), 63 (34.7), 50 (16.2);  $^1H$ -NMR:  $\delta/ppm$  5.43 (d, 1H,  $J = 10.6$  Hz), 5.81 (d, 1H,  $J = 10.6$  Hz), 7.32-8.27 (m, 12H, ArH's); Anal. Calcd. for  $C_{23}H_{14}ClFN_4O_4$ : C, 59.42; H, 3.03; N, 12.05; Found: C, 59.39; H, 3.07; N, 11.98.

*5-(4-Chlorophenyl)-3-(2,4-dichlorophenyl)-1-(4-nitrophenyl)-3a,4,6,6a-tetrahydro-1H,5H-pyrrolo[3,4-c]pyrazole-4,6-dione (7f)*. Yellow crystals; mp. 268-70 °C (from dimethylformamide); yield 90 %; IR:  $\nu/cm^{-1}$  3091.3 (CH-aromatic), 1719.2 (C=O), 1590.9 (C=N); MS, m/z: 520 ( $M^+ + 6$ , 6.3), 518 ( $M^+ + 4$ , 28.6), 516 ( $M^+ + 2$ , 92.1), 514 ( $M^+$ , 100.0), 362 (20.9), 360 (27.6), 335 (49.8), 333 (80.6), 254 (8.0), 252 (24.0), 188 (11.9), 153 (53.4), 125 (57.0), 117 (25.9), 116 (31.3), 90 (74.6), 63 (72.5), 50 (32.8);  $^1H$ -NMR:  $\delta/ppm$  5.55 (d, 1H,  $J = 11.3$  Hz), 5.87 (d, 1H,  $J = 11.3$  Hz), 7.16-8.29 (m, 11H, ArH's); Anal. Calcd. for  $C_{23}H_{13}Cl_3N_4O_4$ : C, 53.56; H, 2.54; N, 10.86; Cl, 20.62; Found: C, 53.64; H, 2.57; N, 10.90; Cl, 20.57.



5-(4-Bromophenyl)-3-(4-fluorophenyl)-1-(4-nitrophenyl)-3a,4,6,6a-tetrahydro-1H,5H-pyrrolo[3,4-c]pyrazole-4,6-dione (**7g**). Yellow crystals; mp. 306-8 °C (from dimethylformamide); yield 96 %; IR:  $\nu/cm^{-1}$  3084.3 (CH-aromatic), 1721.7 (C=O), 1594.8 (C=N); MS, m/z: 510 ( $M^+ + 2$ , 60.6), 508 ( $M^+$ , 69.9), 310 (27.2), 283 (100.0), 237 (26.9), 197 (22.7), 133 (13.9), 116 (25.5), 90 (69.1), 63 (50.5), 50 (22.5);  $^1H$ -NMR:  $\delta/ppm$  5.45 (d, 1H,  $J = 10.8$  Hz), 5.81 (d, 1H,  $J = 10.8$  Hz), 7.31-8.27 (m, 12H, ArH's); Anal. Calcd. for  $C_{23}H_{14}BrFN_4O_4$ : C, 54.24; H, 2.77; N, 11.00; Found: C, 54.15; H, 2.84; N, 10.97.

5-(4-Bromophenyl)-3-(2,4-dichlorophenyl)-1-(4-nitrophenyl)-3a,4,6,6a-tetrahydro-1H,5H-pyrrolo[3,4-c]pyrazole-4,6-dione (**7h**). Yellow crystals; mp. 283-5 °C (from dimethylformamide); yield 93 %; IR:  $\nu/cm^{-1}$  3085.5 (CH-aromatic), 1719.2 (C=O), 1590.9 (C=N); MS, m/z: 564 ( $M^+ + 6$ , 14.7), 562 ( $M^+ + 4$ , 43.2), 560 ( $M^+ + 2$ , 96.4), 558 ( $M^+$ , 73.5), 362 (26.7), 360 (40.3), 335 (59.7), 333 (88.2), 252 (30.7), 197 (35.3), 171 (31.8), 116 (40.0), 90 (100.0), 76 (42.9), 63 (81.2), 50 (34.1);  $^1H$ -NMR:  $\delta/ppm$  5.56 (d, 1H,  $J = 10.3$  Hz), 5.87 (d, 1H,  $J = 10.3$  Hz), 7.15-8.28 (m, 11H, ArH's); Anal. Calcd. for  $C_{23}H_{13}BrCl_2N_4O_4$ : C, 49.31; H, 2.33; N, 10.00; Cl, 12.65; Found: C, 49.50; H, 2.38; N, 10.06; Cl, 12.59.

3,5-Di-(4-fluorophenyl)-1-(4-nitrophenyl)-3a,4,6,6a-tetrahydro-1H,5H-pyrrolo[3,4-c]pyrazole-4,6-dione (**7i**). Yellow crystals; mp. 292-4 °C (from dimethylformamide); yield 96 %; IR:  $\nu/cm^{-1}$  3076.5 (CH-aromatic), 1721.6 (C=O), 1595.3 (C=N); MS, m/z: 448 ( $M^+$ , 100.0), 310 (23.5), 283 (60.5), 237 (21.2), 137 (28.6), 117 (13.1), 109 (40.8), 90 (26.3), 63 (28.1), 50 (20.6);  $^1H$ -NMR:  $\delta/ppm$  5.48 (d, 1H,  $J = 10.9$  Hz), 5.87 (d, 1H,  $J = 10.9$  Hz), 7.32-8.27 (m, 12H, ArH's); Anal. Calcd. for  $C_{23}H_{14}F_2N_4O_4$ : C, 61.60; H, 3.14; N, 12.49; Found: C, 61.52; H, 3.20; N, 12.51.

3-(2,4-Dichlorophenyl)-5-(4-fluorophenyl)-1-(4-nitrophenyl)-3a,4,6,6a-tetrahydro-1H,5H-pyrrolo[3,4-c]pyrazole-4,6-dione (**7j**). Yellow crystals; mp. 244-6 °C (from dimethylformamide); yield 92 %; IR:  $\nu/cm^{-1}$  3081.6 (CH-aromatic), 1718.2 (C=O), 1590.0 (C=N); MS, m/z: 502 ( $M^+ + 4$ , 15.1), 500 ( $M^+ + 2$ , 68.0), 498 ( $M^+$ , 100.0), 362 (17.0), 360 (26.8), 335 (37.5), 333 (56.3), 254 (4.7), 252 (16.2), 137 (34.7), 109 (46.7), 75 (16.6), 63 (24.0), 50 (14.8);  $^1H$ -NMR:  $\delta/ppm$  5.54 (d, 1H,  $J = 11.0$  Hz), 5.85 (d, 1H,  $J = 11.0$  Hz), 7.17-8.30 (m, 11H, ArH's); Anal. Calcd. for  $C_{23}H_{13}Cl_2FN_4O_4$ : C, 55.32; H, 2.62; N, 11.22; Cl, 14.20; Found: C, 55.41; H, 2.65; N, 11.34; Cl, 14.13.

3-(4-Fluorophenyl)-1,5-di-(4-nitrophenyl)-3a,4,6,6a-tetrahydro-1H,5H-pyrrolo[3,4-c]pyrazole-4,6-dione (**7k**). Yellow crystals; mp. 308-10 °C (from dimethylformamide); yield 98 %; IR:  $\nu/cm^{-1}$  3079.4 (CH-aromatic), 1725.2 (C=O), 1595.2 (C=N); MS, m/z: 475 ( $M^+$ , 100.0), 310 (25.2), 283 (60.2), 237 (20.1), 188 (10.5), 134 (12.9), 133 (11.1), 116 (19.2), 90 (46.7), 63 (38.2), 50 (15.6);  $^1H$ -NMR:  $\delta/ppm$  5.57 (d, 1H,  $J = 11.2$  Hz), 5.87 (d, 1H,  $J = 11.2$  Hz), 7.16-8.29 (m, 12H, ArH's); Anal. Calcd. for  $C_{23}H_{14}FN_5O_6$ : C, 58.10; H, 2.96; N, 14.73; Found: C, 57.98; H, 3.06; N, 14.64.

3-(2,4-Dichlorophenyl)-1,5-di-(4-nitrophenyl)-3a,4,6,6a-tetrahydro-1H,5H-pyrrolo[3,4-c]pyrazole-4,6-dione (**7l**). Yellow crystals; mp. 225-7 °C (from acetic acid); yield 93 %; IR:  $\nu/cm^{-1}$  3085.5 (CH-aromatic), 1725.9 (C=O), 1591.9 (C=N); MS, m/z: 529 ( $M^+ + 4$ , 18.5), 527 ( $M^+ + 2$ , 58.2), 525 ( $M^+$ )

(74.6), 362 (25.3), 360 (35.5), 335 (31.4), 333 (46.3), 254 (7.9), 252 (23.9), 189 (32.3), 188 (32.5), 171 (16.5), 158 (28.8), 116 (35.1), 90 (100.0), 76 (49.5), 63 (85.4), 50 (40.6);  $^1\text{H-NMR}$ :  $\delta/\text{ppm}$  5.57 (d, 1H,  $J = 11.6$  Hz), 5.87 (d, 1H,  $J = 11.6$  Hz), 7.16-8.29 (m, 11H, ArH's); Anal. Calcd. for  $\text{C}_{23}\text{H}_{13}\text{Cl}_2\text{N}_5\text{O}_6$ : C, 52.48; H, 2.49; N, 13.30; Cl, 13.47; Found: C, 52.53; H, 2.51; N, 13.38; Cl, 13.34.

*5-(4-Ethylphenyl)-3-(4-fluorophenyl)-1-(4-nitrophenyl)-3a,4,6,6a-tetrahydro-1H,5H-pyrrolo[3,4-c]-pyrazole-4,6-dione (7m)*. Yellow crystals; mp. 282-4 °C (from dimethylformamide); yield 98 %; IR:  $\nu/\text{cm}^{-1}$  3074.3 (CH-aromatic), 2963.0 (CH-aliphatic), 1720.3 (C=O), 1594.5 (C=N); MS, m/z: 458 ( $\text{M}^+$ , 100.0), 310 (16.6), 283 (64.9), 237 (11.6), 132 (38.1), 77 (11.3);  $^1\text{H-NMR}$ :  $\delta/\text{ppm}$  1.18 (t, 3H,  $J = 7.6$  Hz,  $\text{CH}_2\text{CH}_3$ ), 2.58 (q, 2H,  $J = 7.6$  Hz,  $\text{CH}_2\text{CH}_3$ ), 5.44 (d, 1H,  $J = 10.6$  Hz), 5.81 (d, 1H,  $J = 10.6$  Hz), 7.21-8.28 (m, 12H, ArH's);  $^{13}\text{C-NMR}$ :  $\delta/\text{ppm}$  171.49, 170.59 (two C=O amide), 165.24 (d,  $J = 248.7$  Hz, C-F), 148.14, 146.48 (C=N, C- $\text{NO}_2$ ), 144.13, 139.38, 129.58 (d,  $J = 8.4$  Hz, C-*m*-F), 128.89, 127.78, 126.37, 126.00 (d,  $J = 3.1$  Hz, C-*p*-F), 125.04, 115.38 (d,  $J = 22.1$  Hz, C-*o*-F), 112.81, 66.54 (C-5 pyrazoline), 53.81 (C-4 pyrazoline), 27.33 ( $\text{CH}_2\text{CH}_3$ ), 14.78 ( $\text{CH}_2\text{CH}_3$ ); Anal. Calcd. for  $\text{C}_{25}\text{H}_{19}\text{FN}_4\text{O}_4$ : C, 65.49; H, 4.17; N, 12.22; Found: C, 65.48; H, 3.99; N, 12.18.

*3-(2,4-Dichlorophenyl)-5-(4-ethylphenyl)-1-(4-nitrophenyl)-3a,4,6,6a-tetrahydro-1H,5H-pyrrolo[3,4-c]pyrazole-4,6-dione (7n)*. Yellow crystals; mp. 224-6 °C (from dimethylformamide); yield 95 %; IR:  $\nu/\text{cm}^{-1}$  3071.5 (CH-aromatic), 2958.8 (CH-aliphatic), 1719.1 (C=O), 1593.9 (C=N); MS, m/z: 512 ( $\text{M}^+ + 4$ , 9.8), 510 ( $\text{M}^+ + 2$ , 72.5), 508 ( $\text{M}^+$ , 100.0), 360 (23.8), 333 (47.4), 287 (10.4), 252 (18.9), 132 (84.3), 90 (25.7), 77 (16.6), 63 (19.0), 50 (11.5);  $^1\text{H-NMR}$ :  $\delta/\text{ppm}$  1.22 (t, 3H,  $J = 7.6$  Hz,  $\text{CH}_2\text{CH}_3$ ), 2.67 (q, 2H,  $J = 7.6$  Hz,  $\text{CH}_2\text{CH}_3$ ), 5.58 (d, 1H,  $J = 10.4$  Hz), 5.89 (d, 1H,  $J = 10.4$  Hz), 7.21-8.32 (m, 11H, ArH's); Anal. Calcd. for  $\text{C}_{25}\text{H}_{18}\text{N}_4\text{O}_4\text{Cl}_2$ : C, 58.95; H, 3.56; N, 11.00; Cl, 13.92; Found: C, 59.00; H, 3.55; N, 10.98; Cl, 13.94.

### Synthesis of 3,4,5-triaryl-1-(4-nitrophenyl)-2-pyrazoline derivatives 9a-f

This reaction was carried out by the same method described for the preparation of pyrazolines **7** using the  $\alpha,\beta$ -unsaturated ketone arylideneacetophenone derivatives **8a-c** in place of N-arylmaleimides **6**.

*5-Benzoyl-3-(4-fluorophenyl)-1-(4-nitrophenyl)-4-phenyl-2-pyrazoline (9a)*. Yellow crystals; mp. 206-8 °C (from benzene); yield 75 %; IR:  $\nu/\text{cm}^{-1}$  3068.4 (CH-aromatic), 1698.5 (C=O), 1593.2 (C=N); MS, m/z: 466 ( $\text{M}^+ + 1$ , 3.3), 465 ( $\text{M}^+$ , 4.6), 361 (72.0), 360 (100.0), 315 (25.6), 314 (29.3), 105 (13.5), 77 (28.3), 51 (11.7);  $^1\text{H-NMR}$ :  $\delta/\text{ppm}$  5.23 (d, 1H,  $J = 3.0$  Hz), 6.53 (d, 1H,  $J = 3.0$  Hz), 7.13- 8.18 (m, 18H, ArH's); Anal. Calcd. for  $\text{C}_{28}\text{H}_{20}\text{FN}_3\text{O}_3$ : C, 72.24; H, 4.33; N, 9.02; Found: C, 72.71; H, 4.43; N, 9.13.

*5-Benzoyl-3-(2,4-dichlorophenyl)-1-(4-nitrophenyl)-4-phenyl-2-pyrazoline (9b)*. Yellow crystals; mp. 148-50 °C (from benzene-ethanol); yield 71 %; IR:  $\nu/\text{cm}^{-1}$  3064.3 (CH-aromatic), 1699.9 (C=O), 1593.8 (C=N), 1567.8 (C=C); MS, m/z: 517 ( $\text{M}^+ + 2$ , 2.9), 515 ( $\text{M}^+$ ) (3.5), 413 (55.2), 412 (59.4), 411 (91.7), 410 (100.0), 367 (18.9), 366 (20.0), 365 (26.1), 364 (30.3), 165 (14.4), 105 (50.9), 77 (82.1), 50

(16.4);  $^1\text{H-NMR}$ :  $\delta/\text{ppm}$  5.28 (d, 1H,  $J = 3.5$  Hz), 6.58 (d, 1H,  $J = 3.5$  Hz), 7.23- 8.19 (m, 17H, ArH's);  $^{13}\text{C-NMR}$ :  $\delta/\text{ppm}$  192.32 (C=O), 150.30 (C=N), 148.10, 138.68, 136.91, 134.09, 134.00, 132.48, 132.26, 132.01, 129.90, 128.97, 128.77, 128.62, 127.82, 127.18, 127.03, 126.95, 125.28, 112.33 (18C, ArC's), 70.71 (C-5 pyrazoline), 56.54 (C-4 pyrazoline); Anal. Calcd. for  $\text{C}_{28}\text{H}_{19}\text{Cl}_2\text{N}_3\text{O}_3$ : C, 65.12; H, 3.70; N, 8.13; Cl, 13.73; Found: C, 65.32; H, 3.68; N, 8.24; Cl, 13.67.

**5-Benzoyl-4-(4-chlorophenyl)-3-(4-fluorophenyl)-1-(4-nitrophenyl)-2-pyrazoline (9c).** Yellow crystals; mp. 230-2 °C (from benzene-ethanol); yield 68 %; IR:  $\nu/\text{cm}^{-1}$  3063.5 (CH-aromatic), 1692.4 (C=O), 1655.8 (C=N), 1595.2 (C=C); MS, m/z: 502 ( $\text{M}^+ + 2$ , 1.5), 500 ( $\text{M}^+$ , 5.1), 397 (32.4), 395 (100.0), 351 (9.4), 350 (12.2), 349 (30.4), 348 (28.0), 105 (24.9), 77 (40.0), 51 (17.8);  $^1\text{H-NMR}$ :  $\delta/\text{ppm}$  5.31 (d, 1H,  $J = 3.2$  Hz), 6.52 (d, 1H,  $J = 3.2$  Hz), 7.12- 8.17 (m, 17H, ArH's); Anal. Calcd. for  $\text{C}_{28}\text{H}_{19}\text{ClFN}_3\text{O}_3$ : C, 67.26; H, 3.83; N, 8.40; Found: C, 67.11; H, 3.86; N, 8.47.

**5-Benzoyl-4-(4-chlorophenyl)-3-(2,4-dichlorophenyl)-1-(4-nitrophenyl)-2-pyrazoline (9d).** Yellowish orange solid; mp. 204-6 °C (from benzene-ethanol); yield 61 %; IR:  $\nu/\text{cm}^{-1}$  3065.3 (CH-aromatic), 1686.4 (C=O), 1594.8 (C=N), 1557.2 (C=C); MS, m/z: 551 ( $\text{M}^+ + 2$ , 5.4), 549 ( $\text{M}^+$ , 6.5), 515 (5.7), 513 (8.5), 449 (33.1), 447 (100.0), 445 (90.2), 402 (7.7), 401 (19.1), 400 (23.9), 399 (23.9), 105 (34.7), 77 (56.5);  $^1\text{H-NMR}$ :  $\delta/\text{ppm}$  5.41 (d, 1H,  $J = 3.0$  Hz), 6.55 (d, 1H,  $J = 3.0$  Hz), 7.28- 8.36 (m, 16H, ArH's); Anal. Calcd. for  $\text{C}_{28}\text{H}_{18}\text{Cl}_3\text{N}_3\text{O}_3$ : C, 61.05; H, 3.29; N, 7.62; Cl, 19.30; Found: C, 61.10; H, 3.36; N, 7.71; Cl, 19.19.

**5-(4-Bromophenylcarbonyl)-3-(4-fluorophenyl)-1-(4-nitro-phenyl)-4-phenyl-2-pyrazoline (9e).** Yellow solid; mp. 224-6 °C (from benzene); yield 53 %; IR:  $\nu/\text{cm}^{-1}$  3068.6 (CH-aromatic), 1697.3 (C=O), 1655.4 (C=N), 1594.0 (C=N); MS, m/z: 543 ( $\text{M}^+$  3.1), 361 (83.2), 360 (100.0), 315 (26.0), 314 (28.7), 183 (6.5), 91 (7.7), 76 (12.2), 50 (8.6);  $^1\text{H-NMR}$ :  $\delta/\text{ppm}$  5.22 (d, 1H,  $J = 3.3$  Hz), 6.57 (d, 1H,  $J = 3.3$  Hz), 7.13- 8.19 (m, 17H, ArH's); Anal. Calcd. for  $\text{C}_{28}\text{H}_{19}\text{BrFN}_3\text{O}_3$ : C, 61.77; H, 3.51; N, 7.71; Found: C, 61.76; H, 3.55; N, 7.73.

**5-(4-Bromophenylcarbonyl)-3-(2,4-dichlorophenyl)-1-(4-nitrophenyl)-4-phenyl-2-pyrazoline (9f).** Yellow solid; mp. 211-3 °C (from benzene); yield 51 %; IR:  $\nu/\text{cm}^{-1}$  3072.7, 3030.9 (CH-aromatic), 1698.1 (C=O), 1592.2 (C=N);  $^1\text{H-NMR}$ :  $\delta/\text{ppm}$  5.27 (s, br., 1H, 4H-pyrazoline), 6.57 (s, br., 1H, 5H-pyrazoline), 7.24-8.20 (m, 16H, ArH's);  $^{13}\text{C-NMR}$ :  $\delta/\text{ppm}$  191.71 (C=O), 150.29 (C=N), 148.08, 138.73, 136.82, 134.01, 132.29, 131.98, 131.71, 131.51, 130.69, 129.01, 128.49, 127.86, 127.82, 127.09, 127.00, 126.85 125.28, 112.35 (18C, ArC's), 70.63 (C-5 pyrazoline), 56.29 (C-4 pyrazoline); Anal. Calcd. for  $\text{C}_{28}\text{H}_{18}\text{N}_3\text{O}_3\text{BrCl}_2$ : C, 56.49; H, 3.04; N, 7.05; Cl, 11.91; Found: C, 56.48; H, 3.02; N, 7.0; Cl, 11.92.

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