

## Synthesis and Antimicrobial Evaluation of some New Pyrazole, Pyrazoline and Chromeno[3,4-*c*]pyrazole Derivatives

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Alguns novos derivados de pirazol-5-carbonitrila **8,9** e pirazol-5-carboxamida **13** foram sintetizados pela reação de cicloadição de nitriliminas **3,4** a  $\alpha$ -cianocinamonitrilas **5a-f** e  $\alpha$ -cianocinamamida **12a,b**, respectivamente. Por outro lado, a adição de **3,4** a  $\alpha$ -cianocinamato de etila **14a-f** leva à produção de derivados de 2-pirazoline-5-carboxilato de etila, **15, 16**. Também, a cicloadição de **3,4** à 3-cianocumarina **19a** ou à 3-fenilsulfonilcumarina **19b** ou à 3-bromocumarina **19c** leva à produção de derivados do cromeno[3,4-*c*]pirazol-4(3*H*)-ona, **20**. A cicloadição de **3,4** à 3-acetilcumarina, **22** e 3-benzoilcumarina, **23**, produz o correspondente diidrocromeno[3,4-*c*]pirazol-4(3*H*)-ona, **24** e **25**, respectivamente. A oxidação de **24** e **25** produz **20**. A maioria dos compostos preparados mostrou boa a moderada atividade antibacteriana e antifúngica.

Some new pyrazole-5-carbonitrile derivatives **8,9** and pyrazole-5-carboxamide **13** were synthesized by the cycloaddition reaction of nitrilimines **3,4** to  $\alpha$ -cyanocinnamitriles **5a-f** and  $\alpha$ -cyanocinnamamide **12a,b** respectively. On the other hand **3,4** add to ethyl  $\alpha$ -cyanocinnamate **14a-f** to give ethyl 2-pyrazoline-5-carboxylate derivatives **15,16**. Also, cycloaddition of **3,4** to 3-cyanocoumarin **19a** or 3-phenylsulphonylcoumarin **19b** or 3-bromocoumarin **19c** give chromeno[3,4-*c*]pyrazol-4(3*H*)-one derivatives **20**. In the same direction, the cycloaddition of **3,4** to 3-acetylcoumarin **22** and 3-benzoylcoumarin **23** gives the corresponding dihydrochromeno[3,4-*c*]pyrazol-4(3*H*)-one **24** and **25** respectively. Oxidation of **24** and **25** give **20**. Most of the prepared compounds showed good to moderate antibacterial and antifungal activities.

**Keywords:** nitrilimines, pyrazole, pyrazoline, chromeno[3,4-*c*]pyrazole

### Introduction

Pyrazole and heterocyclic fused pyrazole derivatives represent an important class of heterocyclic compounds that have many applications. Some of these compounds are employed as anti-inflammatory compounds,<sup>1-3</sup> as blood platelet aggregation inhibitors,<sup>1</sup> as adenosine antagonists,<sup>4,5</sup> and as controlling herbicides.<sup>6</sup> They also show antimicrobial and antiparasitic activities.<sup>7,8</sup> Also, pyrazoline derivatives have been found to possess antifungal,<sup>9</sup> antidepressant<sup>10-13</sup> anticonvulsant,<sup>12,13</sup> antiinflammatory,<sup>14</sup> antibacterial<sup>15</sup> and anti-tumor<sup>16</sup> activities. Chromenopyrazoles exhibit high activity against gram positive and gram negative bacteria.<sup>17</sup> Moreover, many selectively fluoro-substituted organic compounds show a peculiar pharmacological and

agrochemical properties.<sup>18-23</sup> Therefore, as a connection of our interest in the chemistry of the preparation of heterocyclic compounds from hydrazonoyl halides<sup>24-29</sup> and the above-mentioned findings, the present work is aimed at the preparation of new pyrazole, pyrazoline and their chromene fused derivatives incorporating fluorine and chlorine substituents into these derivatives hoping that it would potentiate their expected biological activities.

### Experimental

Hydrazonoyl bromides **1**<sup>30</sup> and **2**<sup>31</sup> were prepared by known methods. Melting points were measured on electrothermal melting point apparatus and are uncorrected. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. Infrared spectra

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were recorded in potassium bromide pellets on a Pye Unicam SP 3-300 and Shimadzu FT-IR 8101 PC infrared spectrophotometer. NMR spectra were recorded at 200 ( $^1\text{H}$ ) and 50 ( $^{13}\text{C}$ ) MHz in (DMSO- $d_6$ ) on a GEMINI-200 spectrometer. Chemical shifts ( $\delta$ ) are reported relative to TMS as the internal standard. Mass spectra were measured on a GCMS-QP 1000 EX spectrometer operating at an ionization potential of 70 eV.

*Synthesis of 3,4-diaryl-1-(4-nitrophenyl)-1H-pyrazole-5-carbonitriles 8,9*

Triethylamine (0.7 mL, 5 mmol) was added to a stirred solution of the appropriate hydrazonoyl bromides **1,2** and the appropriate  $\alpha$ -cyanocinnamionitrile derivatives **5a-f** (5 mmol) in benzene (40 mL) at room temperature. The mixture was refluxed for 8 h as indicated by TLC. The precipitated triethylamine hydrobromide was removed by filtration and the filtrate was evaporated, and then triturated with methanol. The solid that formed was collected by filtration and crystallized from the suitable solvent to give **8,9** respectively.

*3-(4-Fluorophenyl)-1-(4-nitrophenyl)-4-phenyl-1H-pyrazole-5-carbonitrile 8a*

Obtained as pale yellow crystals; yield: 1.07 g (56%); mp 214-6 °C (from dioxane-ethanol); IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 3119.0, 3083.1 (CH-aromatic), 2235.5 (C $\equiv$ N), 1659.2 (C=N), 1592.7 (C=C);  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  7.04-8.54 (m, 13H, ArH's);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  161.28 (d,  $J$  256.4 Hz, C-F), 146.38, 146.14 (C=N, C- $p$ -NO $_2$ ), 143.10, 138.83, 135.12, 129.76 (d,  $J$  8.3 Hz, C- $m$ -F), 129.25, 127.97, 125.72, 126.52, 125.14, 124.86 (d,  $J$  3.1 Hz, C- $p$ -F), 124.71, 115.50 (d,  $J$  22.1 Hz, C- $o$ -F), 110.61 (C $\equiv$ N); MS,  $m/z$ : 385 ( $M^+$ +1, 88.8), 384 ( $M^+$ , 100.0), 338 (10.3), 337 (15.0), 196 (10.4), 75 (14.5), 63 (13.4). Anal. Calc. for C $_{22}$ H $_{15}$ FN $_4$ O $_2$  ( $M_r$  = 384.36): C, 68.74; H, 3.40; N, 14.57%; Found: C, 68.62; H, 3.39; N, 14.34%.

*3-(2,4-Dichlorophenyl)-1-(4-nitrophenyl)-4-phenyl-1H-pyrazole-5-carbonitrile 9a*

Obtained as off white solid; yield: 1.13 g (52%); mp 160-162 °C (from acetic acid); IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 3085.3 (CH-aromatic), 2228.1 (C $\equiv$ N), 1652.5 (C=N), 1595.1 (C=C);  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  7.01-8.54 (m, 12H, ArH's);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  147.30, 146.38 (C=N, C- $p$ -NO $_2$ ), 145.14, 138.83, 135.12, 133.36, 132.45, 130.33, 130.08, 129.98, 129.45, 129.25, 127.97, 125.72, 126.52, 125.14, 124.71, 110.61 (C $\equiv$ N); MS,  $m/z$ : 436 ( $M^+$ +2, 46.3), 434 ( $M^+$ , 68.1), 401 (38.4), 399 (100.0), 355 (16.4), 353 (48.3), 319 (6.3), 317 (18.7), 246 (17.0),

216 (15.0), 190 (18.6), 127 (23.5), 75 (53.1), 50 (39.2). Anal. Calc. for C $_{22}$ H $_{12}$ Cl $_2$ N $_4$ O $_2$  ( $M_r$  = 435.26): C, 60.70; H, 2.77; N, 12.87; Cl, 16.29%; Found: C, 60.58; H, 2.87; N, 12.69; Cl, 16.31%.

*3-(4-Fluorophenyl)-4-(4-methylphenyl)-1-(4-nitrophenyl)-1H-pyrazole-5-carbonitrile 8b*

Obtained as off white solid; yield: 1.01 g (51%); mp 163-165 °C (from acetic acid); IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 3116.1, 3080.6 (CH-aromatic), 2924.1, 2854.2 (CH-aliphatic), 2233.1 (C $\equiv$ N), 1650.6 (C=N), 1597.0 (C=C);  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  7.02-8.58 (m, 12H, ArH's), 2.25 (s, 3H, CH $_3$ );  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  161.30 (d,  $J$  256.4 Hz, C-F), 146.39, 146.10 (C=N, C- $p$ -NO $_2$ ), 143.13, 138.77, 135.09, 129.78 (d,  $J$  8.3 Hz, C- $m$ -F), 129.28, 128.48, 126.92, 126.51, 125.22, 124.88 (d,  $J$  3.1 Hz, C- $p$ -F), 122.85, 115.52 (d,  $J$  22.1 Hz, C- $o$ -F), 110.58 (C $\equiv$ N), 20.39 (CH $_3$ ); MS,  $m/z$ : 399 ( $M^+$ +1, 71.4), 398 ( $M^+$ , 100.0), 383 (13.5), 351 (10.8), 76 (14.9), 75 (23.2). Anal. Calc. for C $_{23}$ H $_{15}$ FN $_4$ O $_2$  ( $M_r$  = 398.38): C, 69.34; H, 3.79; N, 14.06%; Found: C, 69.14; H, 3.82; N, 13.96%.

*3-(2,4-Dichlorophenyl)-4-(4-methylphenyl)-1-(4-nitrophenyl)-1H-pyrazole-5-carbonitrile 9b*

Obtained as off white solid; yield: 1.16 g (52%); mp 195-197 °C (from acetic acid); IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 3081.2 (CH-aromatic), 2920.3, 2854.8 (CH-aliphatic), 2226.9 (C $\equiv$ N), 1653.1 (C=N), 1595.0 (C=C);  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  7.02-8.54 (m, 11H, ArH's), 2.26 (s, 3H, CH $_3$ );  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  147.32, 146.39 (C=N, C- $p$ -NO $_2$ ), 146.10, 138.77, 135.09, 133.40, 132.44, 130.30, 130.10, 129.96, 129.43, 129.28, 128.48, 126.92, 126.51, 125.22, 122.85 (15C, ArC's), 110.58 (C $\equiv$ N), 20.36 (CH $_3$ ); MS,  $m/z$ : 450 ( $M^+$ +2, 76.8), 448 ( $M^+$ , 100.0), 413 (82.8), 378 (48.1), 367 (42.6), 257 (10.9), 230 (12.6), 165 (11.2), 140 (27.8), 103 (14.7), 90 (21.7), 75 (49.1). Anal. Calc. for C $_{23}$ H $_{14}$ Cl $_2$ N $_4$ O $_2$  ( $M_r$  = 449.28): C, 61.48; H, 3.14; N, 12.47; Cl, 15.78%; Found: C, 61.42; H, 3.21; N, 12.39; Cl, 15.69%.

*3-(4-Fluorophenyl)-4-(4-methoxyphenyl)-1-(4-nitrophenyl)-1H-pyrazole-5-carbonitrile 8c*

Obtained as off white solid; yield: 1.01 g (49%); mp 194-196 °C (from acetic acid); IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 3120.7, 3089.4 (CH-aromatic), 2936.5 (CH-aliphatic), 2231.1 (C $\equiv$ N), 1651.8 (C=N), 1598.6 (C=C);  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  7.03-8.58 (m, 12H, ArH's), 3.77 (s, 3H, OCH $_3$ );  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  161.31 (d,  $J$  256.4 Hz, C-F), 160.82 (C-OCH $_3$ ), 146.39, 146.10 (C=N, C- $p$ -NO $_2$ ), 143.12, 135.11, 129.78 (d,  $J$  8.3 Hz, C- $m$ -F), 129.67, 129.27, 126.51, 125.22, 124.86 (d,  $J$  3.1 Hz, C- $p$ -F), 116.23, 115.52 (d,  $J$  22.1 Hz, C- $o$ -F), 114.54, 110.58

(C≡N), 55.18 (OCH<sub>3</sub>); MS, *m/z*: 414 (M<sup>+</sup>, 100.0), 399 (9.3), 75 (19.8), 74 (17.9). Anal. Calc. for C<sub>23</sub>H<sub>15</sub>FN<sub>4</sub>O<sub>3</sub> (M<sub>r</sub> = 414.38): C, 66.66; H, 3.64; N, 13.52%; Found: C, 66.43; H, 3.61; N, 13.49%.

**3-(2,4-Dichlorophenyl)-4-(4-methoxyphenyl)-1-(4-nitrophenyl)-1H-pyrazole-5-carbonitrile 9c**

Obtained as off white solid; yield: 1.11 g (48%); mp 147-149 °C (from acetic acid); IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 3082.6 (CH-aromatic), 2933.8 (CH-aliphatic), 2224.6 (C≡N), 1652.4 (C=N), 1596.6 (C=C); <sup>1</sup>H NMR (DMSO)  $\delta$  7.01-8.55 (m, 11H, ArH's), 3.78 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>)  $\delta$  159.33 (C-OCH<sub>3</sub>), 148.02, 146.50 (C=N, C-*p*-NO<sub>2</sub>), 141.91, 134.69, 133.41, 133.21, 131.43, 129.00, 128.84, 128.43, 127.39, 124.94, 122.99, 119.88, 114.20, 112.15 (14C, ArC's), 110.78 (C≡N), 54.75 (OCH<sub>3</sub>); MS, *m/z*: 466 (M<sup>+</sup>+2, 62.1), 464 (M<sup>+</sup>, 100.0), 394 (17.5), 76 (18.2), 75 (41.7), 63 (17.4), 62 (16.4), 50 (17.7). Anal. Calc. for C<sub>23</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>3</sub> (M<sub>r</sub> = 465.28): C, 59.37; H, 3.03; N, 12.04; Cl, 15.23%; Found: C, 59.15; H, 3.11; N, 12.14; Cl, 15.31%.

**4-(4-Chlorophenyl)-3-(4-fluorophenyl)-1-(4-nitrophenyl)-1H-pyrazole-5-carbonitrile 8d**

Obtained as off white solid; yield: 1.06 g (51%); mp 160-2 °C (from acetic acid); IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 3113.3, 3079.5 (CH-aromatic), 2231.6 (C≡N), 1656.3 (C=N), 1594.6 (C=C); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  7.03-8.54 (m, 12H, ArH's); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>)  $\delta$  161.33 (d, *J* 256.4 Hz, C-F), 146.42, 146.16 (C=N, C-*p*-NO<sub>2</sub>), 143.18, 137.55, 135.11, 130.09, 129.76 (d, *J* 8.3 Hz, C-*m*-F), 128.88, 126.89, 126.50, 125.20, 124.88 (d, *J* 3.1 Hz, C-*p*-F), 121.05, 115.53 (d, *J* 22.1 Hz, C-*o*-F), 110.61 (C≡N); MS, *m/z*: 419 (M<sup>+</sup>+1, 84.1), 418 (M<sup>+</sup>, 100.0), 371 (10.9), 338 (12.4), 230 (12.6), 95 (10.7), 75 (26.0), 63 (15.7), 50 (19.2). Anal. Calc. for C<sub>22</sub>H<sub>12</sub>ClFN<sub>4</sub>O<sub>2</sub> (M<sub>r</sub> = 418.80): C, 63.09; H, 2.88; N, 13.37; Cl, 8.46%; Found: C, 62.89; H, 2.94; N, 13.29; Cl, 8.52%.

**4-(4-Chlorophenyl)-3-(2,4-dichlorophenyl)-1-(4-nitrophenyl)-1H-pyrazole-5-carbonitrile 9d**

Obtained as white solid; yield: 1.10 g (47%); mp 168-170 °C (from acetic acid); IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 3087.7 (CH-aromatic), 2228.7 (C≡N), 1655.3 (C=N), 1596.6 (C=C); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  7.32-8.56 (m, 11H, ArH's); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>)  $\delta$  148.08, 146.42 (C=N, C-*p*-NO<sub>2</sub>), 146.16, 137.55, 135.11, 133.45, 132.67, 131.87, 130.62, 130.09, 129.87, 129.74, 128.88, 126.89, 126.50, 125.20, 121.05 (15C, ArC's), 110.61 (C≡N); MS, *m/z*: 470 (M<sup>+</sup>+2, 100.0), 468 (M<sup>+</sup>, 92.1), 433 (56.1), 400 (36.8), 387 (41.9), 386 (21.3), 317 (28.1), 289 (19.4), 277 (45.5), 216 (28.9),

177 (22.1), 163 (20.9), 136 (23.3), 100 (26.9), 90 (22.5), 75 (89.7), 63 (83.0), 51 (41.5), 50 (96.8). Anal. Calc. for C<sub>22</sub>H<sub>11</sub>Cl<sub>3</sub>N<sub>4</sub>O<sub>2</sub> (M<sub>r</sub> = 469.70): C, 56.25; H, 2.36; N, 11.92; Cl, 22.64%; Found: C, 56.29; H, 2.35; N, 11.94; Cl, 22.66%.

**3,4-Di-(4-fluorophenyl)-1-(4-nitrophenyl)-1H-pyrazole-5-carbonitrile 8e**

Obtained as yellow crystals; yield: 0.96 g (48%); mp 178-180 °C (from acetic acid); IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 3114.6, 3079.9 (CH-aromatic), 2231.8 (C≡N), 1657.1 (C=N), 1595.1 (C=C); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  7.04-8.58 (m, 12H, ArH's); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>)  $\delta$  164.40 (d, *J* 255.8 Hz, C-F), 161.30 (d, *J* 256.4 Hz, C-F), 146.39, 146.10 (C=N, C-*p*-NO<sub>2</sub>), 143.13, 135.09, 132.74 (d, *J* 8.2 Hz, C-*m*-F), 129.78 (d, *J* 8.3 Hz, C-*m*-F), 129.2, 126.51, 125.22, 124.88 (d, *J* 3.1 Hz, C-*p*-F), 123.72 (d, *J* 3.2 Hz, C-*p*-F), 116.89 (d, *J* 22.4 Hz, C-*o*-F), 115.52 (d, *J* 22.1 Hz, C-*o*-F), 110.58 (C≡N); MS, *m/z*: 403 (M<sup>+</sup>+1, 98.3), 402 (M<sup>+</sup>, 100.0), 356 (10.0), 355 (12.6), 214 (11.9), 75 (19.6). Anal. Calc. for C<sub>22</sub>H<sub>12</sub>F<sub>2</sub>N<sub>4</sub>O<sub>2</sub> (M<sub>r</sub> = 402.35): C, 65.67; H, 3.00; N, 13.92%; Found: C, 65.46; H, 2.96; N, 13.87%.

**3-(2,4-Dichlorophenyl)-4-(4-fluorophenyl)-1-(4-nitrophenyl)-1H-pyrazole-5-carbonitrile 9e**

Obtained as off white solid; yield: 1.04 g (46%); mp 170-172 °C (from acetic acid); IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 3113.3, 3087.4 (CH-aromatic), 2228.1 (C≡N), 1655.9 (C=N), 1596.4 (C=C); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  7.31-8.59 (m, 11H, ArH's); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>)  $\delta$  164.40 (d, *J* 255.8 Hz, C-F), 148.47, 146.39, 146.10 (C=N, C-*p*-NO<sub>2</sub>), 135.09, 133.65, 132.46, 132.74 (d, *J* 8.2 Hz, C-*m*-F), 130.45, 130.21, 129.88, 129.48, 129.2, 126.51, 125.22, 123.72 (d, *J* 3.2 Hz, C-*p*-F), 115.52 (d, *J* 22.1 Hz, C-*o*-F), 110.58 (C≡N); MS, *m/z*: 454 (M<sup>+</sup>+2, 80.8), 452 (M<sup>+</sup>, 100.0), 417 (63.0), 371 (46.8), 335 (16.2), 264 (31.8), 208 (37.0), 145 (35.2), 107 (30.5), 75 (54.7), 63 (45.3), 50 (51.0). Anal. Calc. for C<sub>22</sub>H<sub>11</sub>Cl<sub>2</sub>FN<sub>4</sub>O<sub>2</sub> (M<sub>r</sub> = 453.25): C, 58.29; H, 2.44; N, 12.36; Cl, 15.64%; Found: C, 58.31; H, 2.46; N, 11.34; Cl, 15.66%.

**3-(2,4-Dichlorophenyl)-1,4-di-(4-nitrophenyl)-1H-pyrazole-5-carbonitrile 9f**

Obtained as brown crystals; yield: 1.05 g (44%); mp 220-222 °C (from acetic acid); IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 3086.9 (CH-aromatic), 2233.7 (C≡N), 1594.8 (C=C); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  7.58-8.56 (m, 11H, ArH's); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>)  $\delta$  148.22, 147.37, 146.46 (C=N, 2C-*p*-NO<sub>2</sub>), 145.24, 135.56, 134.02, 133.89, 131.15, 130.31, 130.16, 129.94, 129.38, 128.64, 128.34, 126.78, 125.42, 119.78 (14C, ArC's), 110.61 (C≡N); MS, *m/z*: 481 (M<sup>+</sup>+2, 80.8),

479 (M<sup>+</sup>, 100.0), 398 (92.3), 351 (21.8), 317 (18.5), 215 (21.5), 76 (28.1), 75 (38.1), 63 (29.6), 50 (37.2). Anal. Calc. for C<sub>22</sub>H<sub>11</sub>Cl<sub>2</sub>N<sub>5</sub>O<sub>4</sub> (M<sub>r</sub> = 480.25): C, 55.01; H, 2.47; N, 14.64; Cl, 14.76%; Found: C, 55.00; H, 2.46; N, 14.65; Cl, 14.77%.

*Synthesis of 3,4-diaryl-1-(4-nitrophenyl)-1H-pyrazole-5-carboxamides 13*

This reaction was carried out by the same method described for the preparation of the previous pyrazoles **8,9** using  $\alpha$ -cyanocinnamamide derivatives **12a,b** in place of  $\alpha$ -cyanocinnamitrile derivatives **5a-f**. The prepared compounds **13a,b** together with their physical and spectral data are listed below.

*3-(2,4-Dichlorophenyl)-1-(4-nitrophenyl)-4-phenyl-1H-pyrazole-5-carboxamide 13a*

Obtained as off white solid; yield: 1.04 g (46%); mp 233-235 °C (from acetic acid); IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 3354.9, 3254.1 (NH<sub>2</sub>), 3083.4 (CH-aromatic), 1669.6 (C=O amide), 1627.2 (C=N), 1597.0 (C=C); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  7.18-8.46 (m, 14H, ArH's, NH<sub>2</sub>); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>)  $\delta$  167.78 (C=O amide), 149.38, 145.63 (C=N, C-*p*-NO<sub>2</sub>), 145.12, 133.38, 132.39, 130.03, 129.82, 129.77, 128.39, 127.78, 127.67, 127.02, 126.69, 125.09, 124.87, 124.38, 123.78 (15C, ArC's); MS, *m/z*: 454 (M<sup>+</sup>+2, 65.1), 452 (M<sup>+</sup>, 95.4), 400 (77.8), 354 (51.6), 356 (25.8), 351 (33.7), 190 (26.6), 168 (19.8), 163 (21.2), 115 (26.2), 90 (22.0), 89 (100.0), 76 (36.6), 63 (33.9), 50 (34.5). Anal. Calc. for C<sub>22</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>3</sub> (M<sub>r</sub> = 453.27): C, 58.29; H, 3.11; N, 12.36; Cl, 15.64%; Found: C, 58.31; H, 3.12; N, 12.38; Cl, 15.66%.

*3-(2,4-Dichlorophenyl)-1,4-di-(4-nitrophenyl)-1H-pyrazole-5-carboxamide 13b*

Obtained as pale yellow solid; yield: 1.12 g (45%); mp 182-184 °C (from acetic acid); IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 3301.4, 3228.6 (NH<sub>2</sub>), 3117.5, 3092.1 (CH-aromatic), 1711.0 (C=O amide), 1591.0 (C=C); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  7.42-8.52 (m, 11H, ArH's), 6.25 (s, br., 2H, NH<sub>2</sub>); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>)  $\delta$  167.77 (C=O amide), 149.72, 145.61 (C=N, C-*p*-NO<sub>2</sub>), 145.40, 136.16, 133.38, 132.32, 129.82, 129.79, 128.39, 127.76, 127.53, 127.09, 126.31, 126.23, 124.89, 124.37, 121.78 (15C, ArC's), 21.38 (CH<sub>3</sub>); MS, *m/z*: 499 (M<sup>+</sup>+2, 71.5), 497 (M<sup>+</sup>, 100.0), 462 (12.6), 418 (13.5), 416 (30.5), 362 (16.9), 360 (12.4), 190 (16.0), 88 (11.3), 76 (19.3), 63 (14.4), 50 (17.1). Anal. Calc. for C<sub>22</sub>H<sub>13</sub>Cl<sub>2</sub>N<sub>5</sub>O<sub>5</sub> (M<sub>r</sub> = 498.27): C, 53.02; H, 2.62; N, 14.05; Cl, 14.23%; Found: C, 53.00; H, 2.64; N, 14.07; Cl, 14.22%.

*Synthesis of ethyl 5-cyano-3,4-diaryl-1-(4-nitrophenyl)-2-pyrazoline-5-carboxylates 15,16*

This reaction was carried out by the same method described for the preparation of the previous pyrazoles **8,9** using ethyl  $\alpha$ -cyanocinnamate derivatives **14a-f** in place of  $\alpha$ -cyanocinnamitrile derivatives **5a-f**. Compounds **15,16** with their physical and spectral data are listed below.

*Ethyl 5-cyano-3-(4-fluorophenyl)-1-(4-nitrophenyl)-4-phenyl-2-pyrazoline-5-carboxylate 15a*

Obtained as yellow crystals; yield: 1.19 g (52%); mp 214-215 °C (from acetic acid); IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 3107.7, 3088.4 (CH-aromatic), 2984.3 (CH-aliphatic), 1762.6 (C=O ester), 1592.9 (C=C); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  7.13-8.42 (m, 13H, ArH's), 6.20 (s, 1H pyrazoline), 4.08 (q, 2H, *J* 7.0 Hz, COOCH<sub>2</sub>CH<sub>3</sub>), 0.93 (t, 3H, *J* 7.0 Hz, COOCH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>)  $\delta$  165.17 (d, *J* 256.1 Hz, C-F), 164.38 (C=O ester), 148.26, 146.25 (C=N, C-*p*-NO<sub>2</sub>), 143.43, 132.65, 130.40, 129.37, 129.20 (d, *J* 8.3 Hz, C-*m*-F), 127.25 (d, *J* 3.1 Hz, C-*p*-F), 127.04, 124.73, 120.97, 115.97 (d, *J* 22.2 Hz, C-*o*-F), 111.02 (C≡N), 70.92 (C-5 pyrazoline), 63.35 (C-4 pyrazoline), 61.31 (OCH<sub>2</sub>CH<sub>3</sub>), 12.91 (OCH<sub>2</sub>CH<sub>3</sub>); MS, *m/z*: 459 (M<sup>+</sup>+1, 17.4), 458 (M<sup>+</sup>, 17.0), 386 (100.0), 385 (94.0), 340 (21.2), 339 (21.9), 90 (5.3), 76 (6.6), (21.9), 90 (5.3), 76 (6.6), 51 (4.5), 50 (4.6). Anal. Calc. for C<sub>25</sub>H<sub>19</sub>FN<sub>4</sub>O<sub>4</sub> (M<sub>r</sub> = 458.44): C, 65.49; H, 4.17; N, 12.22 ; Found: C, 65.56; H, 4.26; N, 12.45%.

*Ethyl 5-cyano-3-(2,4-dichlorophenyl)-1-(4-nitrophenyl)-4-phenyl-2-pyrazoline-5-carboxylate 16a*

Obtained as yellow crystals; yield: 1.29 g (51%); mp 203-204 °C (from acetic acid); IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 3066.3 (CH-aromatic), 2995.8, 2926.0 (CH-aliphatic), 1742.7 (C=O ester), 1655.0 (C=N), 1592.6 (C=C); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  7.12-8.43 (m, 12H, ArH's), 6.21 (s, 1H pyrazoline), 4.17 (q, 2H, *J* 7.2 Hz, COOCH<sub>2</sub>CH<sub>3</sub>), 0.95 (t, 3H, *J* 7.2 Hz, COOCH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>)  $\delta$  163.39 (C=O ester), 148.58, 146.13 (C=N, C-*p*-NO<sub>2</sub>), 143.83, 134.05, 133.82, 133.26, 132.48, 130.37, 129.47, 129.17, 128.25, 127.08, 126.88, 124.96, 121.78 (13C, ArC's), 112.98 (C≡N), 70.71 (C-5 pyrazoline), 64.25 (C-4 pyrazoline), 61.24 (OCH<sub>2</sub>CH<sub>3</sub>), 12.84 (OCH<sub>2</sub>CH<sub>3</sub>); MS, *m/z*: 510 (M<sup>+</sup>+2, 9.8), 508 (M<sup>+</sup>, 11.2), 437 (62.4), 435 (100.0), 391 (14.0), 389 (24.7), 219 (8.4), 218 (11.0), 190 (10.4), 90 (15.0), 89 (15.9), 77 (17.0), 76 (20.9), 75 (12.9), 63 (19.0), 51 (15.9), 50 (16.6). Anal. Calc. for C<sub>25</sub>H<sub>18</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>4</sub> (M<sub>r</sub> = 509.34): C, 58.95; H, 3.56; N, 10.99; Cl, 13.92%; Found: C, 58.83; H, 3.58; N, 11.02; Cl, 14.01%.



*Ethyl 5-cyano-3-(4-fluorophenyl)-4-(4-methylphenyl)-1-(4-nitrophenyl)-2-pyrazoline-5-carboxylate 15b*

Obtained as yellow crystals; yield: 1.27 g (54%); mp 187-190 °C (from acetic acid); IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$ : 3188.7 (CH-aromatic), 2983.3, 2961.1 (CH-aliphatic), 1747.1 (C=O ester), 1589.0 (C=C);  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  7.14-8.44 (m, 12H, ArH's), 6.21 (s, 1H pyrazoline), 4.07 (q, 2H,  $J$  7.0 Hz,  $\text{COOCH}_2\text{CH}_3$ ), 2.26 (s, 3H,  $\text{CH}_3$ ), 0.91 (t, 3H,  $J$  7.0 Hz,  $\text{COOCH}_2\text{CH}_3$ );  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  165.17 (d,  $J$  256.1 Hz, C-F), 164.38 (C=O ester), 148.26, 146.25 (C=N, C- $p$ -NO $_2$ ), 143.43, 137.86, 130.88, 129.20 (d,  $J$  8.3 Hz, C- $m$ -F), 128.16, 127.25 (d,  $J$  3.1 Hz, C- $p$ -F), 126.54, 124.73, 120.99, 115.97 (d,  $J$  22.2 Hz, C- $o$ -F), 111.02 (C $\equiv$ N), 70.92 (C-5 pyrazoline), 63.35 (C-4 pyrazoline), 61.31 ( $\text{OCH}_2\text{CH}_3$ ), 21.06 ( $\text{CH}_3$ ), 12.91 ( $\text{OCH}_2\text{CH}_3$ ); MS,  $m/z$ : 473 ( $M^+$ +1, 11.7), 472 ( $M^+$ , 13.8), 400 (89.4), 399 (100.0), 354 (17.6), 353 (20.8), 76 (12.3), 63 (10.7). Anal. Calc. for  $\text{C}_{26}\text{H}_{21}\text{FN}_4\text{O}_5$  ( $M_r = 472.46$ ): C, 66.09; H, 4.48; N, 11.85%; Found: C, 65.89; H, 4.39; N, 11.76%.

*Ethyl 5-cyano-3-(2,4-dichlorophenyl)-4-(4-methylphenyl)-1-(4-nitrophenyl)-2-pyrazoline-5-carboxylate 16b*

Obtained as yellow crystals; yield: 1.36 g (52%); mp 200-203 °C (from acetic acid); IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$ : 3063.7 (CH-aromatic), 2982.3 (CH-aliphatic), 1761.1 (C=O ester), 1651.8 (C=N);  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  7.11-8.42 (m, 11H, ArH's), 6.21 (s, 1H, pyrazoline), 4.11-4.21 (q, 2H,  $J$  7.2 Hz,  $\text{COOCH}_2\text{CH}_3$ ), 2.27 (s, 3H,  $\text{CH}_3$ ), 0.98 (t, 3H,  $J$  7.2 Hz,  $\text{COOCH}_2\text{CH}_3$ );  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  163.37 (C=O ester), 148.61, 146.15 (C=N, C- $p$ -NO $_2$ ), 143.86, 135.66, 134.10, 133.28, 132.45, 130.89, 130.34, 129.48, 129.16, 127.03, 126.82, 124.96, 121.81 (13C, ArC's), 112.86 (C $\equiv$ N), 70.82 (C-5 pyrazoline), 64.31 (C-4 pyrazoline), 61.27 ( $\text{OCH}_2\text{CH}_3$ ), 21.34 ( $\text{CH}_3$ ), 12.84 ( $\text{OCH}_2\text{CH}_3$ ); MS,  $m/z$ : 522 ( $M^+$ , 14.1), 451 (81.4), 449 (100.0), 403 (18.0), 76 (18.0), 75 (15.9), 63 (13.9), 62 (13.3), 50 (12.2). Anal. Calc. for  $\text{C}_{26}\text{H}_{20}\text{Cl}_2\text{N}_4\text{O}_5$  ( $M_r = 523.36$ ): C, 59.66; H, 3.85; N, 10.70; Cl, 13.54%; Found: C, 59.58; H, 3.82; N, 10.68; Cl, 13.49%.

*Ethyl 5-cyano-3-(4-fluorophenyl)-4-(4-methoxyphenyl)-1-(4-nitrophenyl)-2-pyrazoline-5-carboxylate 15c*

Obtained as yellow crystals; yield: 1.19 g (49%); mp 183-184 °C (from acetic acid); IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$ : 3076.8 (CH-aromatic), 2983.3 (CH-aliphatic), 1764.5 (C=O ester), 1597.7 (C=C);  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  7.14-8.43 (m, 12H, ArH's), 6.20 (s, 1H pyrazoline), 4.08 (q, 2H,  $J$  7.2 Hz,  $\text{COOCH}_2\text{CH}_3$ ), 3.76 (s, 3H,  $\text{OCH}_3$ ), 0.90 (t, 3H,  $J$  7.2 Hz,  $\text{COOCH}_2\text{CH}_3$ );  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  165.17 (d,  $J$  256.1 Hz, C-F), 164.38 (C=O ester), 158.10 (C-OCH $_3$ ), 148.26, 146.25 (C=N, C- $p$ -NO $_2$ ), 143.43, 129.20 (d,  $J$  8.3

Hz, C- $m$ -F), 128.23, 127.25 (d,  $J$  3.1 Hz, C- $p$ -F), 126.54, 124.73, 123.17, 121.10, 115.97 (d,  $J$  22.2 Hz, C- $o$ -F), 111.02 (C $\equiv$ N), 70.92 (C-5 pyrazoline), 63.35 (C-4 pyrazoline), 61.31 ( $\text{OCH}_2\text{CH}_3$ ), 54.40 ( $\text{OCH}_3$ ), 12.91 ( $\text{OCH}_2\text{CH}_3$ ); MS,  $m/z$ : 489 ( $M^+$ +1, 5.4), 488 ( $M^+$ , 13.1), 416 (91.5), 415 (100.0), 370 (4.1), 369 (14.2), 77 (10.9), 75 (9.6). Anal. Calc. for  $\text{C}_{26}\text{H}_{21}\text{FN}_4\text{O}_5$  ( $M_r = 488.46$ ): C, 63.92; H, 4.33; N, 11.47%; Found: C, 63.79; H, 4.26; N, 11.41%.

*Ethyl 5-cyano-3-(2,4-dichlorophenyl)-4-(4-methoxyphenyl)-1-(4-nitrophenyl)-2-pyrazoline-5-carboxylate 16c*

Obtained as yellow crystals; yield: 1.26 g (47%); mp 182-184 °C (from acetic acid); IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$ : 3071.8 (CH-aromatic), 2974.7 (CH-aliphatic), 1763.4 (C=O ester), 1651.1 (C=N), 1591.7 (C=C);  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  7.13-8.44 (m, 11H, ArH's), 6.23 (s, 1H pyrazoline), 4.18 (q, 2H,  $J$  7.2 Hz,  $\text{COOCH}_2\text{CH}_3$ ), 3.77 (s, 3H,  $\text{OCH}_3$ ), 0.96 (t, 3H,  $J$  7.2 Hz,  $\text{COOCH}_2\text{CH}_3$ );  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  163.39 (C=O ester), 158.79 (C-OCH $_3$ ), 148.58, 146.13 (C=N, C- $p$ -NO $_2$ ), 143.83, 134.05, 133.26, 132.48, 130.37, 129.47, 128.63, 126.88, 126.49, 124.96, 124.03, 121.78 (12C, ArC's), 112.98 (C $\equiv$ N), 70.71 (C-5 pyrazoline), 64.25 (C-4 pyrazoline), 61.24 ( $\text{OCH}_2\text{CH}_3$ ), 54.50 ( $\text{OCH}_3$ ), 12.84 ( $\text{OCH}_2\text{CH}_3$ ); MS,  $m/z$ : 540 ( $M^+$ +2, 10.9), 538 ( $M^+$ , 14.1), 467 (70.1), 465 (100.0), 421 (8.2), 419 (13.0), 77 (8.4), 76 (11.1), 63 (8.8), 50 (7.4). Anal. Calc. for  $\text{C}_{26}\text{H}_{20}\text{Cl}_2\text{N}_4\text{O}_5$  ( $M_r = 539.36$ ): C, 57.89; H, 3.73; N, 10.38; Cl, 13.14%; Found: C, 57.70; H, 3.78; N, 10.29; Cl, 13.09%.

*Ethyl 4-(4-chlorophenyl)-5-cyano-3-(4-fluorophenyl)-1-(4-nitrophenyl)-2-pyrazoline-5-carboxylate 15d*

Obtained as yellow crystals; yield: 1.15 g (47%); mp 202-203 °C (from acetic acid); IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$ : 3078.7 (CH-aromatic), 2981.4 (CH-aliphatic), 1758.7 (C=O ester), 1589.0 (C=C);  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  7.13-8.42 (m, 12H, ArH's), 6.34 (s, 1H pyrazoline), 4.01 (q, 2H,  $J$  7.1 Hz,  $\text{COOCH}_2\text{CH}_3$ ), 0.90 (t, 3H,  $J$  7.1 Hz,  $\text{COOCH}_2\text{CH}_3$ );  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  165.17 (d,  $J$  256.1 Hz, C-F), 164.38 (C=O ester), 148.26, 146.25 (C=N, C- $p$ -NO $_2$ ), 143.43, 133.08, 131.82, 131.29, 129.20 (d,  $J$  8.3 Hz, C- $m$ -F), 128.48, 127.25 (d,  $J$  3.1 Hz, C- $p$ -F), 124.73, 120.98, 115.97 (d,  $J$  22.2 Hz, C- $o$ -F), 111.03 (C $\equiv$ N), 70.92 (C-5 pyrazoline), 63.35 (C-4 pyrazoline), 61.31 ( $\text{OCH}_2\text{CH}_3$ ), 12.91 ( $\text{OCH}_2\text{CH}_3$ ); MS,  $m/z$ : 493 ( $M^+$ +1, 10.1), 492 ( $M^+$ , 11.5), 420 (88.8), 419 (100.0), 374 (24.5), 373 (25.9), 217 (9.8), 216 (13.3), 122 (13.1), 76 (24.7), 50 (23.0). Anal. Calc. for  $\text{C}_{25}\text{H}_{18}\text{ClFN}_4\text{O}_5$  ( $M_r = 492.88$ ): C, 60.91; H, 3.68; N, 11.36; Cl, 7.19%; Found: C, 60.87; H, 3.66; N, 11.41; Cl, 7.23%.

*Ethyl 4-(4-chlorophenyl)-5-cyano-3-(2,4-dichlorophenyl)-1-(4-nitrophenyl)-2-pyrazoline-5-carboxylate 16d*

Obtained as yellow crystals; yield: 1.38 g (51%); mp 202-204 °C (from acetic acid); IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$ : 3064.3 (CH-aromatic), 2983.2 (CH-aliphatic), 1760.2 (C=O ester), 1652.2 (C=N), 1591.1 (C=C);  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  7.14-8.43 (m, 11H, ArH's), 6.23 (s, 1H pyrazoline), 4.18 (q, 2H,  $J$  7.2 Hz,  $\text{COOCH}_2\text{CH}_3$ ), 0.98 (t, 3H,  $J$  7.2 Hz,  $\text{COOCH}_2\text{CH}_3$ );  $^{13}\text{C NMR}$  (DMSO- $d_6$ )  $\delta$  163.41 (C=O ester), 148.55, 146.11 (C=N, C- $p$ -NO $_2$ ), 143.84, 134.05, 133.68, 133.26, 132.48, 131.54, 131.28, 130.37, 129.47, 128.50, 126.88, 124.96, 121.78 (13C, ArC's), 112.88 (C $\equiv$ N), 70.70 (C-5 pyrazoline), 64.27 (C-4 pyrazoline), 61.22 ( $\text{OCH}_2\text{CH}_3$ ), 12.83 ( $\text{OCH}_2\text{CH}_3$ ); MS,  $m/z$ : 546 ( $M^+$ +4, 3.9), 544 ( $M^+$ +2, 12.5), 542 ( $M^+$ , 10.8), 473 (34.9), 471 (100.0), 469 (98.2), 427 (5.1), 425 (17.0), 423 (18.0), 76 (11.0), 75 (11.3), 63 (8.9), 50 (9.9). Anal. Calc. for  $\text{C}_{25}\text{H}_{17}\text{Cl}_2\text{N}_4\text{O}_4$  ( $M_r = 543.78$ ): C, 55.21; H, 3.15; N, 10.30; Cl, 19.55%; Found: C, 55.23; H, 3.21; N, 10.19; Cl, 19.48%.

*Ethyl 5-cyano-3,4-di-(4-fluorophenyl)-1-(4-nitrophenyl)-2-pyrazoline-5-carboxylate 15e*

Obtained as yellow crystals; yield: 1.47 g (62%); mp 211-213 °C (from acetic acid); IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$ : 3082.9 (CH-aromatic), 2983.4 (CH-aliphatic), 2993.2 (CH-aliphatic), 1758.0 (C=O ester), 1653.9 (C=N), 1591.7 (C=C);  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  7.14-8.43 (m, 12H, ArH's), 6.36 (s, 1H pyrazoline), 4.03-4.14 (q, 2H,  $J$  7.0 Hz,  $\text{COOCH}_2\text{CH}_3$ ), 0.91 (t, 3H,  $J$  7.0 Hz,  $\text{COOCH}_2\text{CH}_3$ );  $^{13}\text{C NMR}$  (DMSO- $d_6$ )  $\delta$  165.17 (d,  $J$  256.1 Hz, C-F), 164.38 (C=O ester), 161.90 (d,  $J$  256.3 Hz, C-F), 148.26, 146.25 (C=N, C- $p$ -NO $_2$ ), 143.43, 130.12 (d,  $J$  8.3 Hz, C- $m$ -F), 129.20 (d,  $J$  8.3 Hz, C- $m$ -F), 126.25 (d,  $J$  3.1 Hz, C- $p$ -F), 124.73, 124.62 (d,  $J$  3.1 Hz, C- $p$ -F), 120.97, 115.97 (d,  $J$  22.2 Hz, C- $o$ -F), 115.64 (d,  $J$  22.0 Hz, C- $o$ -F), 111.02 (C $\equiv$ N), 70.92 (C-5 pyrazoline), 63.35 (C-4 pyrazoline), 61.31 ( $\text{OCH}_2\text{CH}_3$ ), 12.91 ( $\text{OCH}_2\text{CH}_3$ ); MS,  $m/z$ : 476 ( $M^+$ , 13.7), 403 (100.0), 357 (22.7), 76 (10.2), 75 (7.2), 63 (8.0), 50 (6.0). Anal. Calc. for  $\text{C}_{25}\text{H}_{18}\text{F}_2\text{N}_4\text{O}_4$  ( $M_r = 476.43$ ): C, 63.02; H, 3.80; N, 11.76%; Found: C, 62.97; H, 3.85; N, 11.87%.

*Ethyl 5-cyano-3-(2,4-dichlorophenyl)-4-(4-fluorophenyl)-1-(4-nitrophenyl)-2-pyrazoline-5-carboxylate 16e*

Obtained as yellow crystals; yield: 1.55 g (59%); mp 210-212 °C (from dioxane - ethanol); IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$ : 3069.3 (CH-aromatic), 2991.2 (CH-aliphatic), 1747.6 (C=O ester), 1595.1 (C=C);  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  7.11-8.42 (m, 11H, ArH's), 6.36 (s, 1H, 4-H pyrazoline), 4.08-4.19 (q, 2H,  $J$  7.2 Hz,  $\text{COOCH}_2\text{CH}_3$ ), 0.92-0.99 (t, 3H,  $J$  7.2 Hz,  $\text{COOCH}_2\text{CH}_3$ );  $^{13}\text{C NMR}$  (DMSO- $d_6$ )  $\delta$  163.39 (C=O ester), 161.89 (d,  $J$  256.3 Hz, C-F), 148.58, 146.13 (C=N, C- $p$ -NO $_2$ ),

143.83, 134.05, 133.26, 132.48, 130.37, 130.05 (d,  $J$  8.3 Hz, C- $m$ -F), 129.47, 126.88, 124.96, 124.53 (d,  $J$  3.2 Hz, C- $p$ -F), 121.78, 115.45 (d,  $J$  22.1 Hz, C- $o$ -F), 112.98 (C $\equiv$ N), 70.71 (C-5 pyrazoline), 64.25 (C-4 pyrazoline), 61.24 ( $\text{OCH}_2\text{CH}_3$ ), 12.84 ( $\text{OCH}_2\text{CH}_3$ ); MS,  $m/z$ : 528 ( $M^+$ +2, 9.7), 526 ( $M^+$ , 15.4), 455 (68.9), 453 (100.0), 407 (23.5), 107 (10.1), 76 (10.7), 63 (12.1). Anal. Calc. for  $\text{C}_{25}\text{H}_{17}\text{Cl}_2\text{FN}_4\text{O}_4$  ( $M_r = 527.33$ ): C, 56.93; H, 3.24; N, 10.62; Cl, 13.44%; Found: C, 56.97; H, 3.25; N, 10.60; Cl, 13.46%.

*Ethyl 5-cyano-3-(4-fluorophenyl)-1,4-di-(4-nitrophenyl)-2-pyrazoline-5-carboxylate 15f*

Obtained as yellow crystals; yield: 1.33 g (53%); mp 176-178 °C (from acetic acid); IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$ : 3079.0 (CH-aromatic), 2986.3 (CH-aliphatic), 1764.8 (C=O ester), 1654.5 (C=N), 1596.2 (C=C);  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  7.13-8.43 (m, 12H, ArH's), 6.36 (s, 1H pyrazoline), 4.09 (q, 2H,  $J$  7.2 Hz,  $\text{COOCH}_2\text{CH}_3$ ), 0.90 (t, 3H,  $J$  7.2 Hz,  $\text{COOCH}_2\text{CH}_3$ );  $^{13}\text{C NMR}$  (DMSO- $d_6$ )  $\delta$  165.17 (d,  $J$  256.1 Hz, C-F), 164.38 (C=O ester), 148.26, 146.25 (C=N, C- $p$ -NO $_2$ ), 143.43, 129.20 (d,  $J$  8.3 Hz, C- $m$ -F), 127.25 (d,  $J$  3.1 Hz, C- $p$ -F), 124.73, 120.97, 115.97 (d,  $J$  22.2 Hz, C- $o$ -F), 111.04 (C $\equiv$ N), 70.92 (C-5 pyrazoline), 63.35 (C-4 pyrazoline), 61.31 ( $\text{OCH}_2\text{CH}_3$ ), 12.91 ( $\text{OCH}_2\text{CH}_3$ ); MS,  $m/z$ : 503 ( $M^+$ +1, 17.4), 476 (62.3), 430 (100.0), 384 (21.1), 76 (20.1), 63 (12.7), 50 (12.5). Anal. Calc. for  $\text{C}_{25}\text{H}_{18}\text{FN}_5\text{O}_6$  ( $M_r = 503.43$ ): C, 59.64; H, 3.60; N, 13.91%; Found: C, 59.49; H, 3.64; N, 13.87%.

*Synthesis of 1-aryl-3-(4-nitrophenyl)chromeno[3,4-c]pyrazol-4(3H)-ones 20*

To a mixture of hydrazonoyl bromides **1,2** (5 mmol) and 3-cynocoumarin **19a** or 3-phenylsulphonylcoumarin **19b** or 3-bromocoumarin **19c** (5 mmol), in dry benzene (50 mL) at room temperature, triethylamine (0.7 mL, 5 mmol) was added. The mixture was refluxed till the hydrazonoyl bromide disappeared (8 h) as indicated by TLC analysis. After cooling to room temperature, the precipitated triethylamine hydrobromide was filtered and the solvent evaporated. Trituration of the residue with a small amount of methanol gave a crude solid. The latter was collected, washed with methanol and dried. Crystallization from suitable solvent gave the corresponding chromenopyrazoles **20a,b** in good yield. The prepared compounds together with their physical and spectral data are listed below.

*1-(4-Fluorophenyl)-3-(4-nitrophenyl)chromeno[3,4-c]pyrazol-4(3H)-one 20a*

Obtained as brown solid; yield: 0.96 g (48%); mp 310-312 °C (from dioxane); IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$ : 3089.6 (CH-aromatic), 1743.4 (C=O, lactone), 1657.8 (C=N), 1605.0

(C=C);  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  7.32-8.45 (12H, ArH's);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  164.32 (d,  $J$  256.4 Hz, C-F), 156.16 (C=O lactone), 154.31 (C-O), 147.51, 146.24 (C=N, C- $p$ -NO $_2$ ), 142.40, 132.91, 131.29, 129.24 (d,  $J$  8.3 Hz, C- $m$ -F), 128.92, 126.81, 125.58 (d,  $J$  3.1 Hz, C- $p$ -F), 125.17, 124.24, 121.62, 116.12 (d,  $J$  22.2 Hz, C- $o$ -F), 115.91, 112.15; MS,  $m/z$ : 401 (M+, 100.0), 355 (5.9), 257 (49.2), 211 (11.6), 187 (11.7), 163 (18.1), 136 (26.8), 123 (25.5), 90 (52.7), 76 (16.7), 75 (22.1), 63 (43.5), 50 (16.4). Anal. Calc. for C $_{22}$ H $_{12}$ FN $_3$ O $_4$  (M $_r$  = 401.34): C, 65.83; H, 3.01; N, 10.47%; Found: C, 65.81; H, 3.00; N, 10.49%.

*1-(2,4-Dichlorophenyl)-3-(4-nitrophenyl)chromeno[3,4-c]pyrazol-4(3H)-one 20b*

Obtained as brown solid; yield: 1.15 g (51%); mp 232-234 °C (from acetic acid); IR (KBr)  $\nu_{\text{max}}$ /cm $^{-1}$ : 3085.3 (CH-aromatic), 1744.2 (C=O lactone), 1654.8 (C=N), 1592.1 (C=C);  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  7.32-8.45 (11H, ArH's);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  156.16 (C=O lactone), 154.31 (C-O), 147.51, 146.24 (C=N, C- $p$ -NO $_2$ ), 142.40, 133.63, 132.91, 131.54, 131.29, 129.51, 129.49, 128.92, 128.55, 128.42, 126.81, 125.17, 124.24, 121.62, 115.91, 112.17 (16C, ArC's); MS,  $m/z$ : 453 (M $^{+2}$ , 61.0), 451 (M $^+$ , 100.0), 206 (11.3), 177 (14.5), 76 (46.7), 75 (49.9), 63 (19.6), 62 (21.5), 51 (13.8), 50 (48.3). Anal. Calc. for C $_{22}$ H $_{11}$ Cl $_2$ N $_3$ O $_4$  (M $_r$  = 452.24): C, 58.42; H, 2.45; N, 9.29; Cl, 15.67%; Found: C, 58.17; H, 2.47; N, 9.39; Cl, 15.65%.

*Synthesis of 3a-acetyl(benzoyl)-1-aryl-3-(4-nitrophenyl)-3a,9b-dihydrochromeno[3,4-c]-pyrazol-4(3H)-ones 24, 25*

This reaction was carried out by the same method described for the reaction of hydrazonoyl bromides **1,2** with 3-cyanocoumarin **19a** using 3-acetylcoumarin **22** and 3-benzoylcoumarin **23** in place of 3-cyanocoumarin **19a**. Crystallization from the suitable solvent gave the corresponding dihydrochromeno[3,4-c]pyrazole derivatives **24a,b** and **25a,b** respectively in good yield. The prepared compounds together with their physical and spectral data are listed below.

*3a-Acetyl-1-(4-fluorophenyl)-3-(4-nitrophenyl)-3a,9b-dihydrochromeno[3,4-c]-pyrazol-4(3H)-one 24a*

Obtained as off white solid; yield: 1.13 g (51%); mp 288-290 °C (from dimethylformamide-ethanol); IR (KBr)  $\nu_{\text{max}}$ /cm $^{-1}$ : 3107.7 (CH-aromatic), 2985.6 (CH-aliphatic), 1734.8 (C=O lactone), 1712.9 (C=O acetyl), 1595.0 (C=C);  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  7.14-8.31 (m, 11H, ArH's), 6.07 (s, 1H), 2.57 (s, 3H, CH $_3$  acetyl);  $^{13}\text{C}$  NMR (DMSO)  $\delta$  201.55 (C=O acetyl), 164.18 (d,  $J$  256.1 Hz, C-F), 163.85 (C=O lactone), 150.87 (C-O), 149.34, 148.66 (C=N,

C- $p$ -NO $_2$ ), 140.70, 130.17, 130.84 (d,  $J$  8.3 Hz, C- $m$ -F), 127.11, 125.21, 125.00, 124.57 (d,  $J$  3.1 Hz, C- $p$ -F), 116.90, 115.54 (d,  $J$  22.2 Hz, C- $o$ -F), 115.96, 112.80, 78.27 (C-3 coumarin), 54.83 (C-4 coumarin), 25.10 (CH $_3$  acetyl); MS,  $m/z$ : 427 (M $^+$ -18), 401 (100.0), 354 (14.1), 206 (11.5), 76 (30.2), 75 (21.8), 63 (13.0), 50 (20.6). Anal. Calc. for C $_{24}$ H $_{16}$ FN $_3$ O $_5$  (M $_r$  = 445.39): C, 64.71; H, 3.62; N, 9.43%; Found: C, 64.70; H, 3.64; N, 9.42%.

*3a-Acetyl-1-(2,4-dichlorophenyl)-3-(4-nitrophenyl)-3a,9b-dihydrochromeno[3,4-c]-pyrazol-4(3H)-one 24b*

Obtained as yellow solid; yield: 1.31 g (53%); mp 196-197 °C (from acetic acid); IR (KBr)  $\nu_{\text{max}}$ /cm $^{-1}$ : 3107.7 (CH-aromatic), 2989.8 (CH-aliphatic), 1778.0 (C=O), 1712.6 (C=O acetyl), 1590.9 (C=C);  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  7.12-8.27 (m, 11H, ArH's), 6.09 (s, 1H, 4-H coumarin), 2.57 (s, 3H, CH $_3$  acetyl);  $^{13}\text{C}$  NMR (DMSO)  $\delta$  201.53 (C=O acetyl), 163.48 (C=O lactone), 150.68 (C-O), 149.39, 148.09 (C=N, C- $p$ -NO $_2$ ), 140.64, 135.71, 133.54, 132.48, 130.64, 129.72, 129.40, 127.72, 127.24, 125.41, 125.30, 116.86, 114.41, 112.52 (14C, ArC's), 79.19 (C-3 coumarin), 54.84 (C-4 coumarin), 25.02 (CH $_3$  acetyl); MS,  $m/z$ : 497 (M $^{+2}$ , 4.2), 495 (M $^+$ , 6.7), 454 (66.6), 453 (83.1), 452 (83.3), 451 (100.0), 409 (10.7), 408 (15.4), 407 (9.9), 406 (11.8), 373 (17.4), 178 (12.4), 76 (32.7), 50 (30.4). Anal. Calc. for C $_{24}$ H $_{15}$ Cl $_2$ N $_3$ O $_5$  (M $_r$  = 496.29): C, 58.08; H, 3.04; N, 8.46; Cl, 14.28%; Found: C, 57.72; H, 3.06; N, 8.58; Cl, 14.34%.

*3a-Benzoyl-1-(4-fluorophenyl)-3-(4-nitrophenyl)-3a,9b-dihydrochromeno[3,4-c]-pyrazol-4(3H)-one 25a*

Obtained as pale yellow solid; yield: 1.21 g (48%); mp 271-273 °C (from dioxane); IR (KBr)  $\nu_{\text{max}}$ /cm $^{-1}$ : 3089.4 (CH-aromatic), 1735.3 (C=O), 1655.8 (CO benzoyl), 1594.5 (C=C);  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  7.15-8.13 (m, 17H, ArH's), 6.38 (s, 1H, 4-H coumarin);  $^{13}\text{C}$  NMR (DMSO)  $\delta$  197.55 (C=O benzoyl), 164.18 (d,  $J$  256.1 Hz, C-F), 162.85 (C=O lactone), 150.92 (C-O), 149.23, 148.68 (C=N, C- $p$ -NO $_2$ ), 140.70, 132.63, 131.87, 131.31, 130.17, 130.84 (d,  $J$  8.3 Hz, C- $m$ -F), 127.73, 127.10, 125.18, 125.02, 124.57 (d,  $J$  3.1 Hz, C- $p$ -F), 116.90, 116.27 (d,  $J$  22.2 Hz, C- $o$ -F), 115.96, 112.87, 78.27 (C-3 coumarin), 54.83 (C-4 coumarin); MS,  $m/z$ : 507 (M $^+$ , 53.0), 401 (11.9), 257 (100.0), 211 (12.6), 163 (20.0), 136 (28.2), 123 (66.7), 105 (20.9), 90 (39.3), 77 (34.7), 63 (25.1), 51 (16.1), 50 (13.4). Anal. Calc. for C $_{29}$ H $_{18}$ FN $_3$ O $_5$  (M $_r$  = 507.46): C, 68.63; H, 3.57; N, 8.28%; Found: C, 68.60; H, 3.56; N, 8.27%.

*3a-Benzoyl-1-(2,4-dichlorophenyl)-3-(4-nitrophenyl)-3a,9b-dihydrochromeno[3,4-c]-pyrazol-4(3H)-one 25b*

Obtained as yellow solid; yield: 1.31 g (47%); mp 193-195 °C (from dioxane); IR (KBr)  $\nu_{\text{max}}$ /cm $^{-1}$ : 3072.0 (CH-



aromatic), 1769.3 (br., C=O lactone, benzoyl), 1671 (C=N), 1586.1 (C=C);  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  7.13-8.24 (m, 16H, ArH's), 6.36 (s, 1H, 4-H coumarin);  $^{13}\text{C NMR}$  (DMSO)  $\delta$  197.53 (C=O benzoyl), 162.85 (C=O lactone), 150.52 (C-O), 149.20, 148.13 (C=N, C-*p*-NO $_2$ ), 140.72, 135.69, 133.31, 132.91, 132.66, 131.76, 131.30, 130.81, 129.76, 129.68, 127.96, 127.70, 126.87, 125.32, 125.12, 116.93, 115.82, 112.73 (18C, ArC's), 78.27 (C-3 coumarin), 54.83 (C-4 coumarin); MS,  $m/z$ : 559 ( $M^+$ +2, 3.2), 557 ( $M^+$ , 10.1), 453 (66.2), 451 (100.0), 405 (11.7), 307 (8.3), 206 (15.5), 178 (18.0), 177 (19.1), 151 (18.9), 105 (30.1), 76 (75.4), 75 (83.8), 63 (31.2), 51 (31.9), 50 (79.1). Anal. Calc. for C $_{29}$ H $_{17}$ Cl $_2$ N $_3$ O $_5$  ( $M_r$  = 558.36): C, 62.37; H, 3.06; N, 7.52; Cl, 12.69%; Found: C, 62.38; H, 3.06; N, 7.51; Cl, 12.68%.

#### Oxidation of chromeno[3,4-*c*]pyrazol-4(3*H*)-one derivatives **24** and **25**

##### General procedure

A suspension of the products **24a** or **25a** (5 mmol) in aqueous potassium hydroxide (10 mL, 10%) was refluxed for 12 h. The reaction mixture was cooled, poured into water (50 mL) and acidified with hydrochloric acid (4 mL, mol L $^{-1}$ ). The crude product was filtered, washed with water, dissolved in toluene (10 mL) and refluxed for 2 h. After cooling, the product that precipitated was collected and crystallized from suitable solvent. The pure products were identical in all aspects (mp, mixed mp and spectroscopic data) with **20a**. Similarly, oxidation of **24b** or **25b** gave compound **20b**.

## Results and Discussion

1,3-Dipolar cycloaddition of nitrilimines **3,4**, prepared *in situ* from hydrazonyl bromides **1,2** in dry benzene in the presence of triethylamine, to  $\alpha$ -cyanocinnamitriles **5a-f** was carried out at reflux for 8 h,<sup>24</sup> and gave exclusively 3,4-diaryl-1-(4-nitrophenyl)pyrazole-5-carbonitriles **8a-e**, **9a-f** respectively (Scheme 1).

The intermediate pyrazolines **6,7** were not detected in any case. The structures of the isolated products **8,9** were elucidated by their elemental analyses and spectroscopic data. The  $^1\text{H NMR}$  revealed, in each case, the absence of signals assignable to the 4-CH and 5-CH protons of the corresponding pyrazoline derivatives **6,7** and **10,11**<sup>32</sup> and the IR spectra of the products **8,9** show a nitrile absorption band at about 2224-2235 cm $^{-1}$ . This finding suggests that the 5,5-dicyano-2-pyrazoline derivatives **6,7** are easily aromatized by thermal elimination of hydrogen cyanide to give **8,9**. Such elimination is analogous to the thermal elimination of hydrazoic acid<sup>33</sup> from 5-azido-5-benzoyl-

1,3,4-triphenyl-2-pyrazolin and of benzenesulfinic acid<sup>32</sup> from 5-benzenesulfonyl-1,3,4-triphenyl-2-pyrazoline.

The signals of  $^{13}\text{C NMR}$  spectra of **8b** and **9c** are compatible with the proposed structure. Thus, they display a signal of methyl carbon at 20.39 and of methoxy carbon at 54.75 ppm. The C $\equiv$ N signals appear at 110.58 and 110.78 ppm respectively.

The regiochemistry of **8,9** was confirmed by comparison of the properties of **8a** with the pertinent regioisomer 3-(4-fluorophenyl)-1-(4-nitrophenyl)-5-phenylpyrazole-4-carbonitrile **7**, which was prepared from the reaction of **1** with phenacyl cyanide.<sup>34</sup>

Similarly, the reaction of **1,2** with  $\alpha$ -cyanocinnamamide **12a,b** in benzene at reflux temperature gave the corresponding pyrazole derivatives **13a,b** (Scheme 1). Like the previous reaction, thermal elimination of hydrogen cyanide took place. The structures of the products were confirmed considering the correct elemental analyses and spectroscopic data (Experimental part).

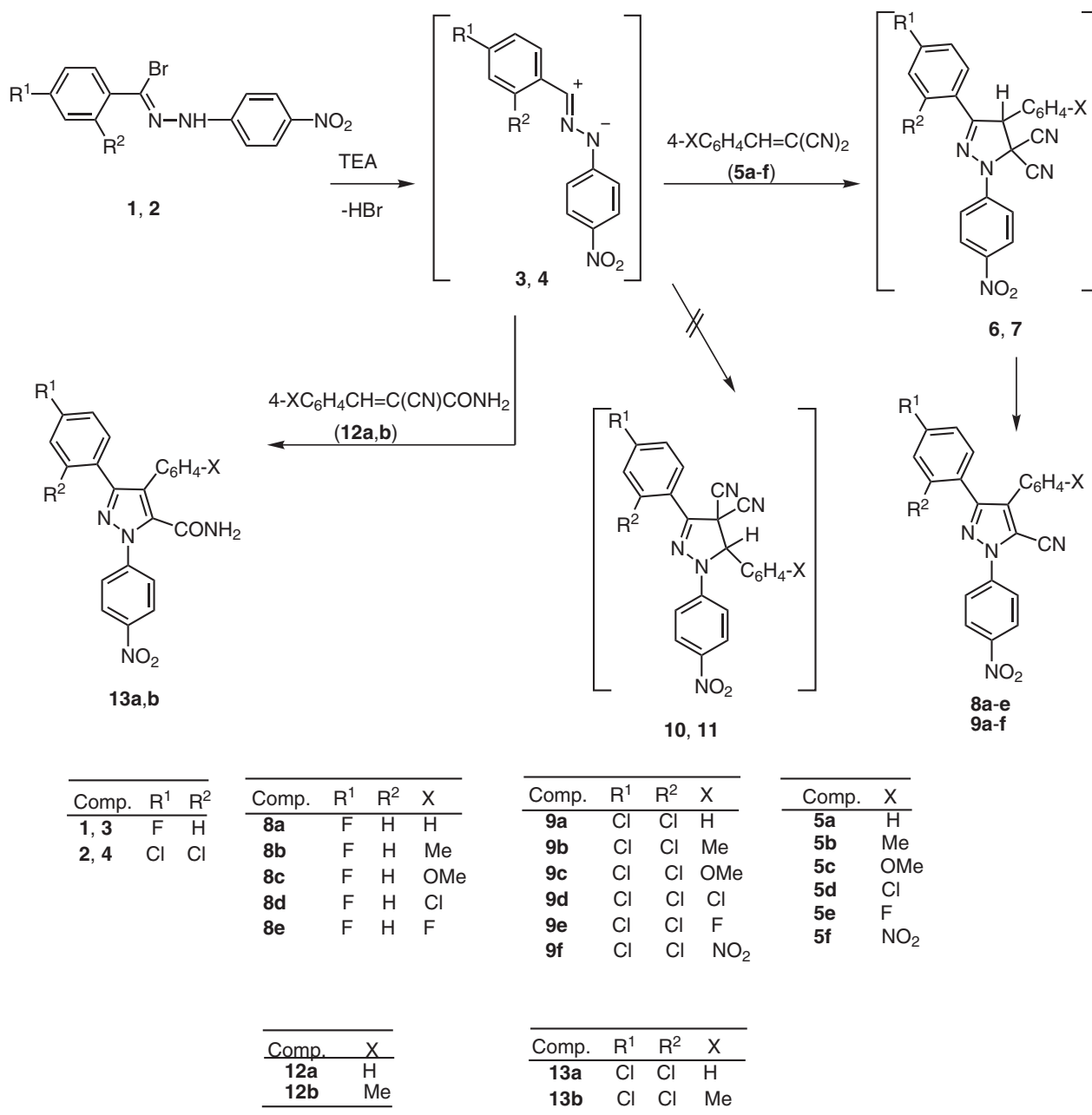
The  $^1\text{H NMR}$  spectra of the products **13** showed no signal due to 4-CH characteristic of 2-pyrazoline derivative (Experimental part). This result confirms the elimination of hydrogen cyanide.

The reaction of the ethyl  $\alpha$ -cyanocinnamates **14a-f** with the **1,2** when carried out in a similar manner, gave the corresponding 2-pyrazoline derivatives **15,16** (Scheme 2).

The thermal elimination of hydrogen cyanide from the reaction products **15,16** was not observed. The structure of the products was in agreement with their elemental analyses and spectroscopic data. Although compounds **15,16** bear a nitrile group its IR absorption band does not appear similar to the case of aliphatic nitriles activated by a nitrogen or oxygen atom in the  $\alpha$ -position.<sup>35,36</sup> This similarity of the absence of the nitrile absorption in the IR spectra together with the chemical shift value 6.2 ppm observed for the methine proton also exclude the possibility of the other regioisomer **17,18** for the isolated product. This is because compounds of type **17,18** are expected to exhibit strong nitrile absorption in their IR spectra<sup>37</sup> and their methine chemical shift at the 5-position would appear at upper field (5.1 ppm).<sup>38</sup> The decisive evidence for the existence of the nitrile group is provided by the  $^{13}\text{C NMR}$  of compounds **15,16**. Undoubtedly the signals at 112.02-112.98 ppm are attributed to nitrile carbon atoms. The mass spectra of compounds **15,16** show the correct molecular ions and the most important fragmentation pathways of the molecular ion involve generation of [ $M - 73$  (COOC $_2$ H $_5$ )] $^+$  ions (base peaks). Another common fragment results from loss of NO $_2$  and give [ $M - 73 - 46$ ] $^+$  ions.

Also, the reaction of 3-cyanocoumarin **19a** with hydrazonyl bromides **1,2** in refluxing benzene in the



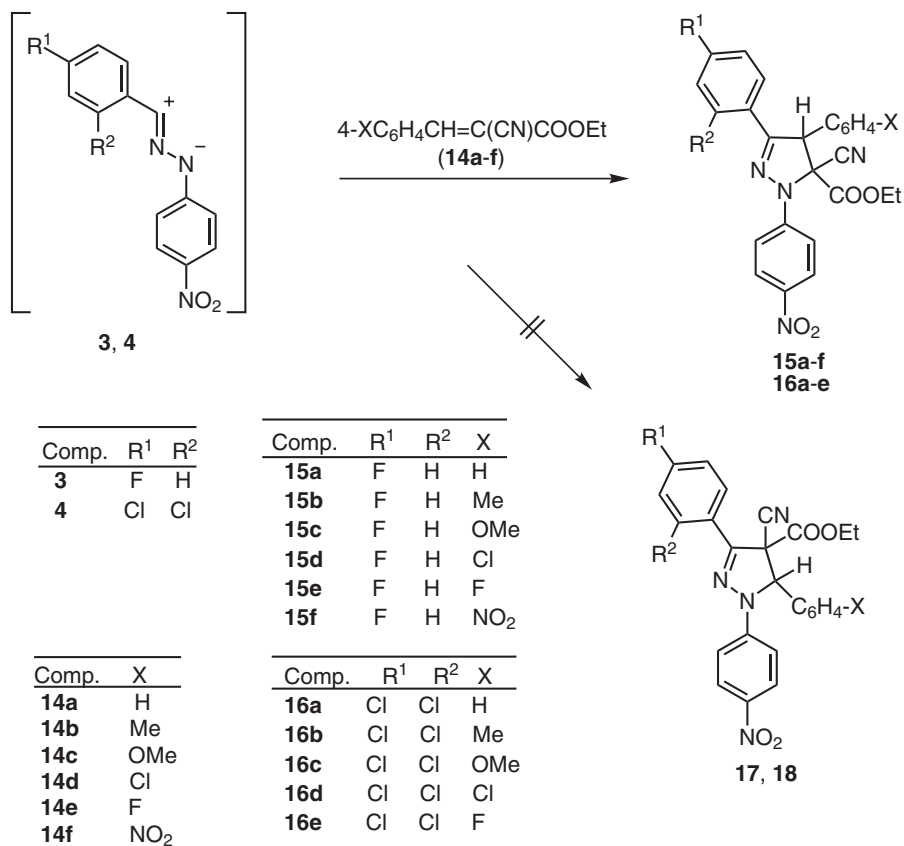


Scheme 1.

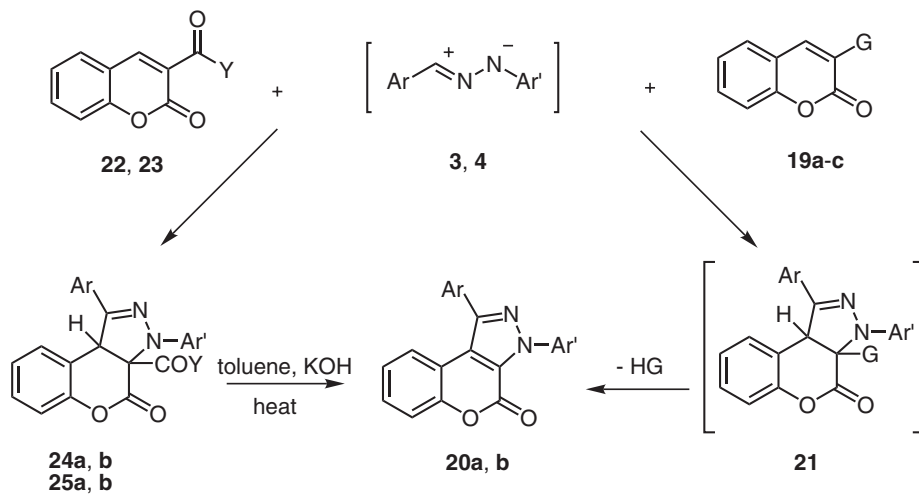
presence of triethylamine gave only one isolable product in each case **20a** and **20b** which analyzed correctly for the proposed structures. The <sup>1</sup>H NMR spectra of **20a,b** revealed the absence of the methine 9b hydrogen in the cycloadducts **21a,b** (Scheme 3) and the IR spectrum showed the absence of the cyano group absorption band. These results indicate that the cycloadducts **21a,b** undergo simultaneous elimination of hydrogen cyanide as soon as it is formed to give 1-aryl-3-(4-nitrophenyl)chromeno[3,4-*c*]pyrazol-4(3*H*)-one derivatives **20a,b**.

The products **20a,b** were also formed via cycloaddition of the nitrilimines **3,4** to 3-phenylsulfonylcoumarin **19b** or 3-bromocoumarin **19c**. The products **20a,b** result undoubtedly via thermal elimination of benzenesulfinic acid and hydrogen bromide from the corresponding cycloadducts (Scheme 3).

The reaction of hydrazonoyl bromides **1,2** with acetylcoumarin **22** and benzoylcoumarin **23** in refluxing benzene in the presence of triethylamine afforded the 1,3-dipolar cycloadducts 1-aryl-3-(4-nitrophenyl)-3aR-



Scheme 2.



a: Ar = 4-FC<sub>6</sub>H<sub>4</sub>; b: Ar = 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>

G: **19a**, CN; **19b**, SO<sub>2</sub>Ph; **19c**, Br

**22, 24**, Y = CH<sub>3</sub>

**23, 25**, Y = Ph

Scheme 3.

3a,9b-dihydrochromeno[3,4-c]pyrazole-4(3*H*)-ones **24a,b** and **25a,b** respectively (Scheme 3). The assigned structures **24a,b** and **25a,b** were supported by analytical and spectroscopic data (Experimental part). In their <sup>1</sup>H NMR spectra, they have characteristic signals due to 9b proton resonance near 6.0 and 6.3 ppm, respectively. The chemical shifts seem to be compatible with the assigned structures **24a,b** and **25a,b** and exclude the possibility of the other regioisomer. The <sup>13</sup>C NMR of compound **24b** taken as example, displays two characteristic signals of carbonyl carbon of acetyl group and lactone at 201.53 and 163.48 ppm respectively. The signals at 79.19, 54.84 and 25.02 are attributed to C-3a, C-9b and methyl carbon of acetyl group. The structures of the products were also confirmed by their conversion to **20a,b**. Thus, by refluxing **24a,b** or **25a,b** in aqueous potassium hydroxide (10%) followed by heating the crude product in toluene gave, in both cases, **20a,b** (Scheme 3).

#### Biological activity

Antibacterial and antifungal screening was carried out using the agar diffusion technique.<sup>39</sup> Most of the newly

synthesized compounds were tested for their antibacterial activity in vitro against several pathogenic bacterial strains such as gram-negative, *Escherichia coli*, *Enterobacter aerogenes*, *Pseudomonas aeruginosa*, *Klebsiella oxytoca*, gram-positive, *Staphylococcus aureus*, and their antifungal activity against the fungi *Candida albicans* and *Aspergillus flavus* at a concentration 200 µg mL<sup>-1</sup> using DMSO as a solvent. DMSO showed no inhibition zone. Erythromycin (Himedia, India, LOT NO.0000008821), Cephalixin (Himedia, India, LOT NO.0000010511), Tetracycline, (Himedia, India, LOT NO.0000014267) and Flucoral were used as reference substances. The results are illustrated in Table 1 as average diameter of inhibition zone in mm.

As shown in the table most of the tested pyrazoles and pyrazolines showed low to moderate activities against *E. coli*. Against *P. aeruginosa* the pyrazole derivatives were found to have higher activity than pyrazoline derivatives. It is noticed that only pyrazoline derivatives possess moderate to high activity against *S. aureus*, and among them the compounds have fluorophenyl group at position 3 of pyrazole or at position 1 of chromeno[3,4-c]pyrazole were more effective than those that have dichlorophenyl group. Also,

**Table 1.** Antimicrobial screening result of the tested compounds

Compound	Inhibition zone diameter (mm per 200 mcg sample)						
	<i>C. albicans</i>	<i>A. flavus</i>	<i>E. Coli</i>	<i>P. aeruginosa</i>	<i>E. aerogenes</i>	<i>S. aureus</i>	<i>K. oxytoca</i>
DMSO	-	-	-	-	-	-	-
<b>8a</b>	-	-	11	13	-	-	12
<b>9a</b>	-	-	-	14	-	-	-
<b>9b</b>	-	-	14	-	-	-	-
<b>8c</b>	-	12	12	8	6	-	7
<b>8d</b>	-	-	12	13	-	-	11
<b>9d</b>	-	-	-	13	-	-	-
<b>8e</b>	-	-	15	-	-	-	13
<b>9e</b>	-	-	12	14	-	-	-
<b>9f</b>	-	-	-	-	-	-	-
<b>15b</b>	9	-	13	9	-	18	14
<b>16b</b>	-	-	16	-	-	11	14
<b>16d</b>	12	-	12	8	11	-	-
<b>15e</b>	8	-	14	9	-	14	14
<b>16e</b>	-	-	-	-	-	12	13
<b>15f</b>	11	-	-	12	10	16	12
<b>20a</b>	14	-	8	-	9	-	12
<b>20b</b>	-	-	12	-	-	11	-
<b>24b</b>	8	-	12	-	-	-	12
<b>25a</b>	10	-	8	-	-	19	-
<b>25b</b>	13	-	11	-	6	-	-
Erythromycin <sup>a</sup>	-	-	14	15	13	12	30
Cephalixin <sup>b</sup>	-	-	15	-	14	15	25
Tetracyclin <sup>b</sup>	-	-	18	-	15	15	20
Flucoral	16	14	-	-	-	-	-

<sup>a</sup>15 µg mL<sup>-1</sup>; <sup>b</sup>30 µg mL<sup>-1</sup>.

the activity against *C. albicans* and *E. aerogenes* was noticed for pyrazolines and fused pyrazolines rather than pyrazoles or fused pyrazoles. On the other hand, most of the tested pyrazoles and pyrazolines exhibited moderate activity against *K. oxytoca*, but it is obvious that among pyrazole derivatives, the active compounds were the fluorinated ones. None of the tested compounds except **8c** inhibits the growth of *A. flavus*. Compound **9f** showed no inhibitory effect against any of the tested organisms. It is important to mention that compound **9f** is the only pyrazole derivative that have nitro group on phenyl substituent at position 4.

## Conclusions

Different pyrazole derivatives, as well as pyrazoline derivatives and their chromenofused derivatives were synthesized, completely characterized and evaluated for their antibacterial and antifungal activities.

The test results have evidenced that the pyrazoline and fused pyrazoline compounds have higher activities than the pyrazole and fused pyrazole ones.

Concerning the substitution in pyrazole **8a**, **8c**, **8d**, **8e**, **15b**, **15e**, **15f** and pyrazoline compounds **9a**, **9b**, **9d**, **9e**, **9f**, **16b**, **16e** at the phenyl group in 3-position demonstrated that the fluorosubstituted compounds are more effective than the chlorosubstituted analogues, and compound **16d** was exception to this trend.

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