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SYNTHESIS AND ANTI-HBV ACTIVITY OF 4-AMINOANTI-PYRINE DERIVATIVES

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The reactions of 4-aminoantipyrine with acetylacetone, ethyl acetoacetate, morpholine, piperazine, and ethyl cyanoacetate were studied. All structures were determined by ^{1}H NMR and mass spectroscopy techniques.

Keywords: acetylacetone, 4-aminoantipyrine, ethyl acetoacetate, antiviral activity, diazotization.

The syntheses of 4-aminoantipyrine derivatives have attracted the attention of several research groups due to their potential biological activities [1]. In this context, a broad spectrum of bioactive 4-aminoantipyrine derivatives has been investigated, and diverse bioactivities such as analgesic [2, 3], anti-inflammatory [3], antimicrobial [4-6], and anticancer [7] have been reported.

As part of our continuing interest in the synthesis of potential bioactive compounds [8-10], we undertook the syntheses of 4-aminoantipyrine derivatives in our search for antiviral agents. In this work we describe our results concerning the syntheses and anti-hepatitis B activity of these substances.

In the present work, we investigated the reaction of 4-aminoantipyrine **1** with acetylacetone, ethyl acetoacetate, morpholine, piperazine, or ethyl cyanoacetate, which afforded compounds **2**–**5** in 65–78% yields. The nitrile derivative **5** [11] was treated with acetylacetone in the presence of triethylamine at reflux temperature to afford the carbonitrile **6** in 73% yield. The reaction of compound **5** with acetylacetone started with condensation followed by a cyclization step.

The treatment of 1,5-dimethyl-4-(4-oxopentan-2-ylideneamino)-2-phenyl-1,2-dihydropyrazol-3-one **2** with phenyl isothiocyanate, aniline, Schiff base, ethyl cyanoacetate, malononitrile, and aromatic aldehydes gave compounds **7**-**12** in 55-71% yields.

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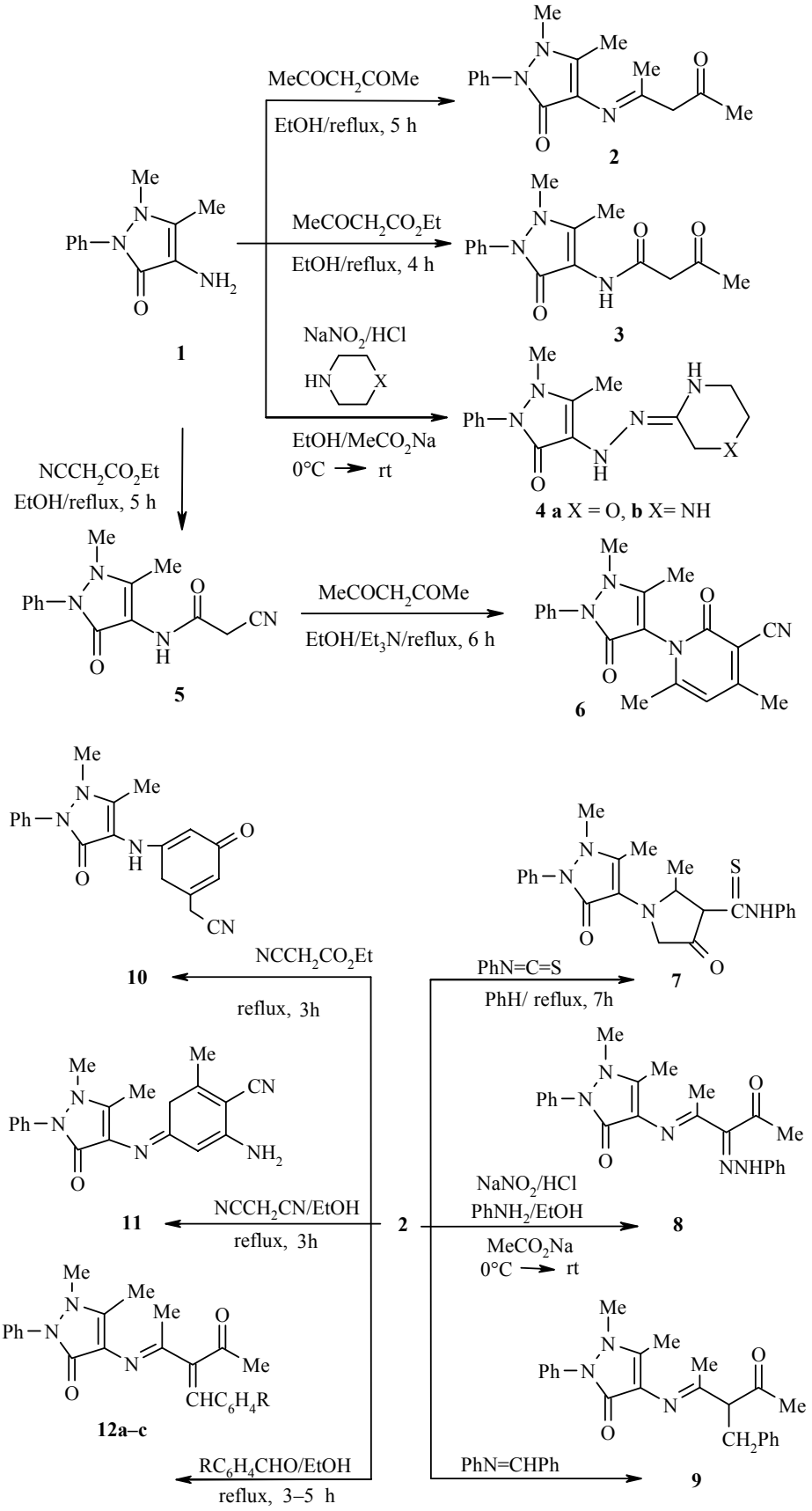
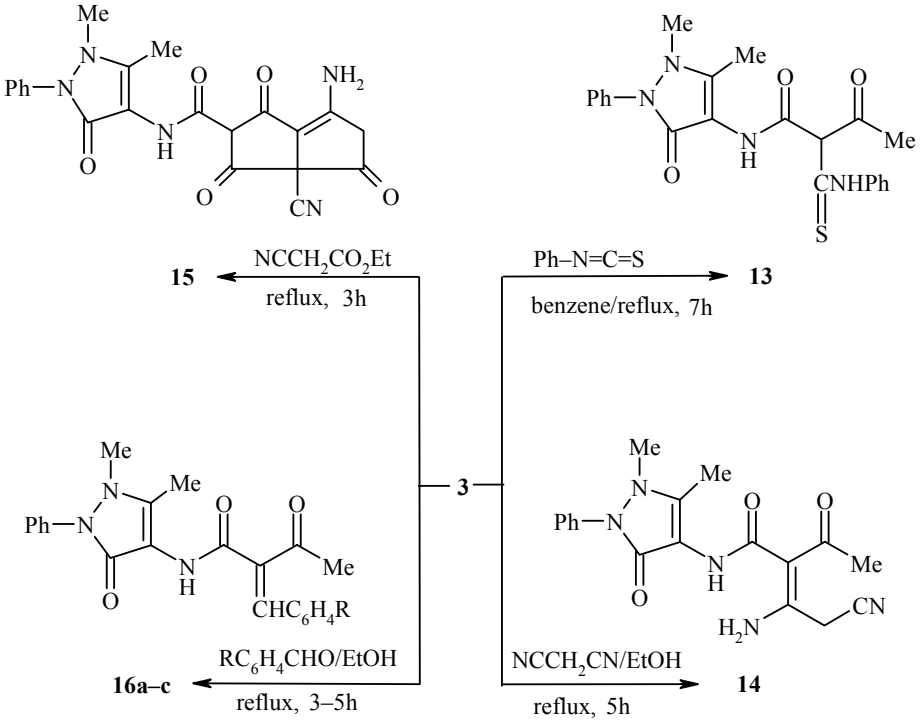


12 a R = H, **b** R = *p*-OMe, **c** R = *o*-OH

The treatment of N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-3-oxobutanamide **3** with phenyl isothiocyanate, malononitrile, ethyl cyanoacetate, or aromatic aldehydes afforded compounds **13-16** in 57–84% yields.



16 a R = H, **b** R = *p*-OMe, **c** R = *o*-OH

The structures of compounds **2-16** were confirmed by ^{1}H NMR and IR spectroscopy, and mass spectrometry. In the ^{1}H NMR spectra of the synthesized compounds we observed all the proton signals of the aromatic ring, heterocyclic ring, methyl groups, and proton of NH group.

A preliminary viral screening against hepatitis B virus (HBV) (Hep G2 2.2.15 cell method) [12-15] indicated that compounds **6**, **7**, **10**, and **11** are active against HBV replication with IC_{50} 80-90 μM and CC_{50} 78-88 μM, while compounds **2**–**5**, **8, 9**, and **12a**–**c** showed moderate viral replication inhibition and moderate cytotoxicity. The drug *Lamivudine*, which is a potent selective inhibitor of HBV replication [15], was used as a standard for the comparative studies.

EXPERIMENTAL

Melting points were determined using a Kofler block instrument. IR (KBr disks) spectra were recorded on a Pie-Unicam SP-1100 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AC 250 FT NMR spectrometer at 250 MHz in DMSO-d_6, with TMS as an internal standard. ES mass spectra were obtained from an Esquire 3000 plus ion-trap mass spectrometer from Bruker Daltonics. The microanalyses were performed at the microanalytical unit, Cairo University, Egypt. Antiviral activity against HBV of the synthesized compounds was conducted at the National Liver Institute, Menoufia University, Shebin El-Koam, Egypt.

Compounds 2, 3, and 5 (General Method). A mixture of 4-aminoantipyrine **1** (10.15 g, 0.05 mol) in an excess of acetylacetone, ethyl acetoacetate, or ethyl cyanoacetate was refluxed for 6 h. The reaction mixture was cooled to room temperature, and the formed solid product was collected by filtration and recrystallized from ethanol to afford compounds **2**, **3**, and **5** in 67-78% yields.

1,5-Dimethyl-4-(4-oxopentan-2-ylideneamino)-2-phenyl-1,2-dihydropyrazol-3-one (2). Yield 11.11 g (78%); mp 138-140°C. IR spectrum, ν, cm^{-1}: 3300 (NH), 1685, 1710 (C=O). ^1H NMR spectrum, δ, ppm: 7.70-7.32 (5H, m, H Ar); 3.18 (3H, s, NCH_3); 2.50 (2H, s, CH_2); 2.45 (3H, s, CH_3); 1.99 (3H, s, $COCH_3$); 0.99 (3H, s, CH_3). Mass spectrum, *m/z* (*I*, %): 285 $[M]^+$ (75), 286 $[M + H]^+$ (60). Found, %: C 67.21; H 6.90; N 14.58. $C_{16}H_{19}N_3O_2$. Calculated, %: C 67.35; H 6.71; N 14.73.

N-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-3-oxobutanamide (3). Yield 9.61 g (67%); mp 130-132°C. IR spectrum, ν, cm^{-1}: 3310 (NH), 1680, 1700 (C=O). ^1H NMR spectrum, δ, ppm: 9.28 (1H, br. s, NH); 7.62-7.34 (5H, m, H Ar); 3.33 (2H, s, CH_2); 3.10 (3H, s, NCH_3); 2.19 (3H, s, CH_3); 2.07 (3H, s, $COCH_3$). Mass spectrum, *m/z* (*I*, %): 287 $[M]^+$ (100), 288 $[M + H]^+$ (44). Found, %: C 62.60; H 6.11; N 14.57. $C_{15}H_{17}N_3O_3$. Calculated, %: C 62.71; H 5.96; N 14.63.

N-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-cyanoacetamide (5). Yield 9.45 g (70%), lit. [11] 57%.

Compounds 4a,b (General Method). A mixture of 4-aminoantipyrine **1** (2.03 g, 0.01 mol) in the appropriate amounts of cold HCl and $NaNO_2$ was added to a solution of the appropriate active methylene compound (0.01 mol) dissolved in ethanol (20 ml) and sodium acetate (1.5 g). The reaction mixture was left for 3 h at room temperature and the formed solid product was filtered off, washed several times with water, and recrystallized from ethanol to give compounds **4a,b**.

1,5-Dimethyl-4-[2-(morpholin-3-ylidene)hydrazinyl]-2-phenyl-1,2-dihydropyrazol-3-one (4a). Yield 2.31 g (77%); mp 255-256°C. IR spectrum, ν, cm^{-1}: 3300 (NH), 1675 (C=O). ^1H NMR spectrum, δ, ppm: 7.52-7.31 (5H, m, H Ar); 7.02 (1H, br. s, NH); 3.63 (2H, m, CH_2); 3.40 (2H, m, CH_2); 3.12 (3H, s, NCH_3); 2.81 (2H, m, CH_2); 2.09-1.98 (4H, m, CH_3, NH). Mass spectrum, *m/z* (*I*, %): 301 $[M]^+$ (100), 302 $[M + H]^+$ (71). Found, %: C 59.63; H 6.20; N 23.11. $C_{15}H_{19}N_5O_2$. Calculated, %: C 59.79; H 6.36; N 23.24.

1,5-Dimethyl-2-phenyl-4-[2-(piperazin-2-ylidene)hydrazinyl]-1,2-dihydropyrazol-3-one (4b). Yield 1.95 g (65%); mp 243-246°C. IR spectrum, ν, cm^{-1}: 3300 (NH), 1665 (C=O). ^1H NMR spectrum, δ, ppm: 7.50-7.32 (5H, m, H Ar); 7.05 (1H, br. s, NH); 3.10 (3H, s, NCH_3); 2.84 (2H, m, CH_2); 2.79 (2H, m, CH_2); 2.61 (2H, m, CH_2); 2.15–1.97 (4H, m, CH_3, NH). Mass spectrum, *m/z* (*I*, %): 300 $[M]^+$ (100), 301 $[M + H]^+$ (28). Found, %: C 59.90; H 6.60; N 27.88. $C_{15}H_{20}N_6O$. Calculated, %: C 59.98; H 6.71; N 27.98.

1-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (6). A mixture of compound **5** (2.70 g, 0.01 mol), absolute ethanol (20 ml), acetylacetone (0.01 mol), and triethylamine (0.5 ml) was refluxed for 6 h. The reaction mixture was allowed to cool to room temperature and the formed solid product was filtered off and recrystallized from ethanol to afford compound **6** (2.43 g, 73%); mp 230–232°C. IR spectrum, ν, cm^{-1}: 3300 (NH), 2200 (CN), 1690 (C=O). ^1H NMR spectrum, δ, ppm: 7.52-7.33 (5H, m, H Ar); 6.50 (1H, s, pyridinone); 3.17 (3H, s, NCH_3); 2.21 (3H, s, CH_3); 1.84 (3H, s, CH_3); 1.74 (3H, s, CH_3). Mass spectrum, *m/z* (*I*, %): 334 $[M]^+$ (100). Found, %: C 68.19; H 5.33; N 16.65. $C_{19}H_{18}N_4O_2$. Calculated, %: C 68.25; H 5.43; N 16.76.

N-Phenyl-1-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-methyl-4-oxopyrrolidine-3-carbothioamide (7). A mixture of compound **2** (2.85 g, 0.01 mol), dry benzene (15 ml), and phenyl isothiocyanate (0.01 mol) was refluxed for 7 h. The reaction mixture was allowed to cool to room temperature and the formed solid product was filtered off and recrystallized from methanol to afford compound **7** (2.73 g, 65%); mp 207-209°C. IR spectrum, ν, cm^{-1}: 3440 (NH), 1665 (C=O). ^1H NMR spectrum, δ, ppm: 7.35-7.29 (5H, m, H Ar); 7.19-6.92 (5H, m, H Ar); 4.00 (1H, br. s, NH); 3.80 (2H, s, CH_2); 3.13 (3H, s, NCH_3); 3.00 (1H, m, CH); 2.61 (1H, m, CH); 1.80 (3H, s, CH_3); 1.14 (3H, s, CH_3). Mass spectrum, *m/z* (*I*, %): 420 $[M]^+$ (65). Found, %: C 65.53; H 5.66; N 13.16. $C_{23}H_{24}N_4O_2S$. Calculated, %: C 65.69; H 5.75; N 13.33.

1,5-Dimethyl-4-[4-oxo-3-(2-phenylhydrazono)pentan-2-ylideneamino]-2-phenyl-1,2-dihydropyrazol-3-one (8). As mentioned before for compounds **4a,b** (2.72 g, 70%); mp 180-182°C. IR spectrum, ν, cm^{-1}: 3435 (NH), 1669 (C=O). ^1H NMR spectrum, δ, ppm: 11.00 (1H, br. s, NH); 7.42-7.32 (5H, m, H Ar); 7.04-6.94 (5H, m, H Ar); 3.19 (3H, s, NCH_3); 2.50 (3H, s, CH_3); 2.20 (3H, s, $COCH_3$); 0.99 (3H, s, CH_3). Mass spectrum, *m/z*

(*I*, %): 389 $[M]^+$ (54), 390 $[M + H]^+$ (60). Found, %: C 67.60; H 5.81; N 17.80. $C_{22}H_{23}N_5O_2$. Calculated, %: C 67.85; H 5.95; N 17.98.

4-(3-Benzyl-4-oxopentan-2-ylideneamino)-1,5-dimethyl-2-phenyl-1,2-dihydropyrazol-3-one (9). A mixture of compound **2** (2.85 g, 0.01 mol), (*E*)-N-benzyli- denebenzeneamine (0.01 mol), and absolute ethanol (15 ml) was refluxed for 6 h. The reaction mixture was cooled to room temperature and the formed solid product was filtered off and recrystallized from ethanol to afford compound **9** (2.47 g, 66%); mp 171-173°C. IR spectrum, ν, cm^{-1}: 3400 (NH), 1660 (C=O). ^1H NMR spectrum, δ, ppm: 7.52-7.37 (5H, m, H Ar); 7.25-7.11 (5H, m, H Ar); 3.18 (3H, s, NCH_3); 3.04 (2H, m, CH_2); 2.70 (1H, m, CH); 2.44 (3H, s, CH_3); 2.07 (3H, s, $COCH_3$); 0.92 (3H, s, CH_3). Mass spectrum, *m/z* (*I*, %): 375 $[M]^+$ (88), 376 $[M + H]^+$ (12). Found, %: C 73.44; H 6.60; N 11.08. $C_{23}H_{25}N_3O_2$. Calculated, %: C 73.57; H 6.71; N 11.19.

[5-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-ylamino)-3-oxo-cyclohexa-1,4-dienyl]-acetonitrile (10). A mixture of compound **2** (2.85 g, 0.01 mol) in an excess of ethyl cyanoacetate was refluxed for 3 h. The reaction mixture was cooled to room temperature and the formed solid product was filtered off and recrystallized from ethanol to afford compound **10** (2.17 g, 65%); mp 230-232°C. IR spectrum, ν, cm^{-1}: 3500 (NH), 2200 (CN), 1670 (C=O). ^1H NMR spectrum, δ, ppm: 7.30-7.09 (5H, m, H Ar); 6.32 (1H, s, CH); 5.83 (1H, s, CH); 3.13 (3H, s, NCH_3); 3.02 (2H, m, CH_2); 2.62 (2H, m, CH_2); 2.17 (3H, s, CH_3); 2.02 (1H, br. s, NH). Mass spectrum, *m/z* (*I*, %): 334 $[M]^+$ (45), 335 $[M + H]^+$ (78). Found, %: C 68.18; H 5.34; N 16.59. $C_{19}H_{28}N_4O_2$. Calculated, %: C 68.25; H 5.43; N 16.76.

6-Amino-4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-ylimino)-2-methylcyclohexa-1,5-dienecarbonitrile (11). A mixture of compound **2** (2.85 g, 0.01 mol), malononitrile (0.01 mol), and absolute ethanol (15 ml) was refluxed for 3 h. The reaction mixture was cooled to room temperature, and the formed solid product was filtered off and recrystallized from ethanol to afford compound **11** (1.83 g, 55%); mp 250-252°C. IR spectrum, ν, cm^{-1}: 3300 (NH), 2200 (CN), 1675 (C=O). ^1H NMR spectrum, δ, ppm: 7.40-7.22 (5H, m, H Ar); 4.85 (2H, br. s, NH_2); 3.95 (1H, s, CH); 3.17 (3H, s, NCH_3); 2.37 (3H, s, CH_3); 2.00 (2H, s, CH_2); 1.75 (3H, s, CH_3). Mass spectrum, *m/z* (*I*, %): 333 $[M]^+$ (77), 334 $[M + H]^+$ (48). Found, %: C 68.34; H 5.66; N 21.11. $C_{19}H_{19}N_5O$. Calculated, %: C 68.45; H 5.74; N 21.01.

Compounds 12a-c (General Method). A mixture of compound **2** (2.85 g, 0.01 mol), the appropriate aldehyde (0.01 mol), and ethanol (25 ml) was heated under reflux for 3–5 h. The reaction mixture was cooled to room temperature and the formed solid product was filtered off and recrystallized from ethanol to afford compounds **12a-c**.

4-(3-Benzylidene-4-oxopentan-2-ylideneamino)-1,5-dimethyl-2-phenyl-1,2-dihydropyrazol-3-one (12a). Yield 2.23 g (60%); mp 160-162°C. IR spectrum, ν, cm^{-1}: 3300 (NH), 1660 (C=O). ^1H NMR spectrum, δ, ppm: 7.50-7.34 (6H, m, H Ar, CH); 7.25-7.04 (5H, m, H Ar); 3.16 (3H, s, NCH_3); 2.44 (3H, s, CH_3); 2.39 (3H, s, $COCH_3$); 0.96 (3H, s, CH_3). Mass spectrum, *m/z* (*I*, %): 373 $[M]^+$ (100), 374 $[M + H]^+$ (58). Found, %: C 73.85; H 6.09; N 11.15. $C_{23}H_{23}N_3O_2$. Calculated, %: C 73.97; H 6.21; N 11.25.

4-[3-(4-Methoxybenzylidene)-4-oxopentan-2-ylideneamino]-1,5-dimethyl-2-phenyl-1,2-dihydro-pyrazol-3-one (12b). Yield 2.86 g (71%); mp 171-173°C. IR spectrum, ν, cm^{-1}: 3250 (NH), 1668 (C=O). ^1H NMR spectrum, δ, ppm: 8.34-8.22 (2H, m, H Ar); 7.50-7.22 (6H, m, H Ar, CH); 7.19-7.04 (2H, m, H Ar); 3.85 (3H, s, OCH_3); 3.19 (3H, s, NCH_3); 2.40 (3H, s, CH_3); 2.30 (3H, s, $COCH_3$); 0.92 (3H, s, CH_3). Mass spectrum, *m/z* (*I*, %): 373 $[M]^+$ (100), 403 $[M + H]^+$ (44). Found, %: C 71.34; H 6.12; N 10.22. $C_{24}H_{25}N_3O_3$. Calculated, %: C 71.44; H 6.25; N 10.41.

4-[3-(4-Hydroxybenzylidene)-4-oxopentan-2-ylideneamino]-1,5-dimethyl-2-phenyl-1,2-dihydro-pyrazol-3-one (12c). Yield 2.45 g (63%); mp 198–200°C. IR spectrum, ν, cm^{-1}: 3230 (NH), 1665 (C=O). ^1H NMR spectrum, δ, ppm: 9.80 (1H, br. s, OH); 7.50-7.22 (6H, m, H Ar, CH); 7.19-6.97 (4H, m, H Ar); 3.16 (3H, s, NCH_3); 2.43 (3H, s, CH_3); 2.33 (3H, s, $COCH_3$); 0.92 (3H, s, CH_3). Mass spectrum, *m/z* (*I*, %): 389 $[M]^+$. Found, %: C 70.80; H 5.81; N 10.60. $C_{23}H_{23}N_3O_3$. Calculated, %: C 70.93; H 5.95; N 10.79.

N-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-3-oxo-2-(phenylcarbamothioyl)-butanamide (13). As mentioned before for compound **7** (3.12 g, 74%); mp 195-197°C. IR spectrum, ν, cm^{-1}: 3200 (NH), 1685 (C=O). ^{1}H NMR spectrum, δ, ppm: 9.30 (1H, br. s, NH); 7.30-7.20 (5H, m, H Ar); 7.10-6.95 (5H, m, H Ar); 4.09 (1H, br. s, NH); 3.30 (1H, s, CH); 3.11 (3H, s, NCH_3); 2.18 (3H, s, CH_3); 2.06 (3H, s, $COCH_3$). Mass spectrum, *m/z* (*I*, %): 422 $[M]^+$ (45). Found, %: C 62.39; H 5.19; N 13.18. $C_{22}H_{22}N_4O_3S$. Calculated, %: C 62.54; H 5.25; N 13.26.

N-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-acetyl-3-amino-4-cyanobut-2-enamide (14). As mentioned before for compound **11** (2.64 g, 75%); mp 240-242°C. IR spectrum, ν, cm^{-1}: 3320 (NH), 2210 (CN), 1655 (C=O). ^{1}H NMR spectrum, δ, ppm: 9.74 (1H, br. s, NH); 7.30-7.22 (5H, m, H Ar); 3.14 (3H, s, NCH_3); 3.06 (2H, s, CH_2); 2.30 (3H, s, $COCH_3$); 2.19 (3H, s, CH_3); 2.00 (2H, br. s, NH_2). Mass spectrum, *m/z* (*I*, %): 353 $[M]^+$ (60). Found, %: C 61.00; H 5.23; N 19.63. $C_{18}H_{19}N_5O_3$. Calculated, %: C 61.18; H 5.42; N 19.82.

N-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-6-amino-3a-cyano-1,3,4-trioxo-1,2,3,3a,4,5-hexahydropentalene-2-carboxamide (15). As mentioned before for compound **10** (2.38 g, 57%); mp 224-226°C. IR spectrum, ν, cm^{-1}: 3450 (NH), 2210 (CN), 1660 (C=O). ^{1}H NMR spectrum, δ, ppm: 9.26 (1H, br. s, NH); 7.50-7.29 (5H, m, H Ar); 4.15 (1H, s, CH); 3.17, 3.11 (5H, 2s, NCH_3, CH_2); 2.17 (3H, s, CH_3); 2.02 (2H, br. s, NH_2). Mass spectrum, *m/z* (*I*, %): 419 $[M]^+$ (34), 420 $[M + H]^+$ (28). Found, %: C 60.00; H 3.93; N 16.55. $C_{21}H_{17}N_5O_5$. Calculated, %: C 60.14; H 4.09; N 16.70.

Compounds 16a–c (General method). As mentioned before for compounds **12a–c**.

N-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-benzylidene-3-oxo-butanamide (16a). Yield 3.00 g (80%); mp 170–172°C. IR spectrum, ν, cm^{-1}: 3350 (NH), 1670 (C=O). ^{1}H NMR spectrum, δ, ppm: 9.70 (1H, br. s, NH); 8.25 (1H, s, CH); 7.55–7.34 (10H, m, H Ar, CH); 3.11 (3H, s, NCH_3); 2.30 (3H, s, $COCH_3$); 2.20 (3H, s, CH_3). Mass spectrum, *m/z* (*I*, %): 375 $[M]^+$ (90), 376 $[M + H]^+$ (54). Found, %: C 70.18; H 5.60; N 11.25. $C_{22}H_{21}N_3O_3$. Calculated, %: C 70.38; H 5.64; N 11.19.

N-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-(4-methoxybenzylidene)-3-oxo-butanamide (16b). Yield 3.16 g (78%); mp 155-157°C. IR spectrum, ν, cm^{-1}: 3290 (NH), 1665 (C=O). ^{1}H NMR spectrum, δ, ppm: 9.70 (1H, br. s, NH); 8.30-8.22 (3H, m, H Ar, CH); 7.50-7.22 (5H, m, H Ar); 7.18-7.00 (2H, m, H Ar); 3.80 (3H, s, OCH_3); 3.13 (3H, s, NCH_3); 2.30 (3H, s, $COCH_3$); 2.20 (3H, s, CH_3). Mass spectrum, *m/z* (*I*, %): 405 $[M]^+$ (50). Found, %: C 68.00; H 5.59; N 10.22. $C_{23}H_{23}N_3O_4$. Calculated, %: C 68.13; H 5.72; N 10.36.

N-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-(4-hydroxybenzylidene)-3-oxobutanamide (16c). Yield 3.28 g (84%); mp 175-177°C. IR spectrum, ν, cm^{-1}: 3270 (NH), 1665 (C=O). ^{1}H NMR spectrum, δ, ppm: 9.77 (2H, br. s, OH, NH); 8.30 (1H, s, CH); 7.50–7.22 (5H, m, H Ar, CH); 7.14-6.98 (4H, m, H Ar); 3.15 (3H, s, NCH_3); 2.30 (3H, s, $COCH_3$); 2.20 (3H, s, CH_3). Mass spectrum, *m/z* (*I*, %): 391 $[M]^+$ (55). Found, %: C 67.39; H 5.20; N 10.86. $C_{22}H_{21}N_3O_4$. Calculated, %: C 67.51; H 5.41; N 10.74.

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