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NOVEL SYNTHESIS OF HIGHLY FUNCTIONALIZED PYRAZOLONE SYSTEMS *VIA* REARRANGEMENT OF 5-PHENYL-1-OXA-5,6-DIAZASPIRO[2.4]HEPTANE-4,7-DIONES

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Epoxidation of 4-alkylidene(arylidene)-1-phenyl-3,5-pyrazolidinediones using alkaline hydrogen peroxide gave the corresponding 5-phenyl-1-oxa-5,6-diazaspiro[2.4]heptane-4,7-dione derivatives. Their reaction with nucleophilic reagents was investigated. The resulting products depend on the type of the diazaspiro compound and/or the nucleophile used.

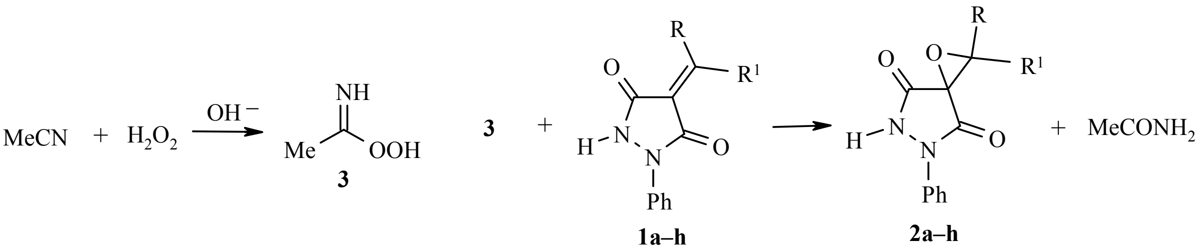
Keywords: 3,5-pyrazolidinediones, epoxidation, ^{15}N NMR, ring transformation.

1-Phenyl-3,5-pyrazolidinedione condenses readily with carbonyl compounds in refluxing dioxane or glacial acetic acid to yield 4-alkylidene(arylidene)-1-phenyl-3,5-pyrazolidinediones **1a-h** [1-4].

The exocyclic olefinic bond at position 4 in derivatives **1a-h** is highly reactive towards oxidation using hydrogen peroxide in alkaline medium to give 5-phenyl-1-oxa-5,6-diazaspiro[2.4]heptane-4,7-dione derivatives **2a-h**. Smooth oxidations with high yield were achieved using acetonitrile as a solvent. The experimental facts lead to the reaction mechanism proposed in Scheme 1.

Acetonitrile and alkaline hydrogen peroxide forms peroxycarboximidic acid (**3**) [5-8], which reacts with the 4-exocyclic double bond in **1a-h** to give 5-phenyl-1-oxa-5,6-diazaspiro[2.4]heptane-4,7-dione derivatives **2a-h**. Attempts to use a peroxycarboxylic acid in the oxidation of **1** failed. Peroxycarboxylic acids are electrophilic oxidizing agents that are unreactive towards the α,β-unsaturated carbonyl derivatives **1** [9-14].

Scheme1



1,**2** **a** R = R^1 = Me, **b** R+R^1 = $(CH_2)_5$, **c–h** R = H, **c** R^1 = Ph, **d** R^1 = 4-MeC_6H_4, **e** R^1 = 2-$MeOC_6H_4$, **f** R^1 = 4-ClC_6H_4, **g** R^1 = 2-$O_2NC_6H_4$, **h** R^1 = 4-$O_2NC_6H_4$

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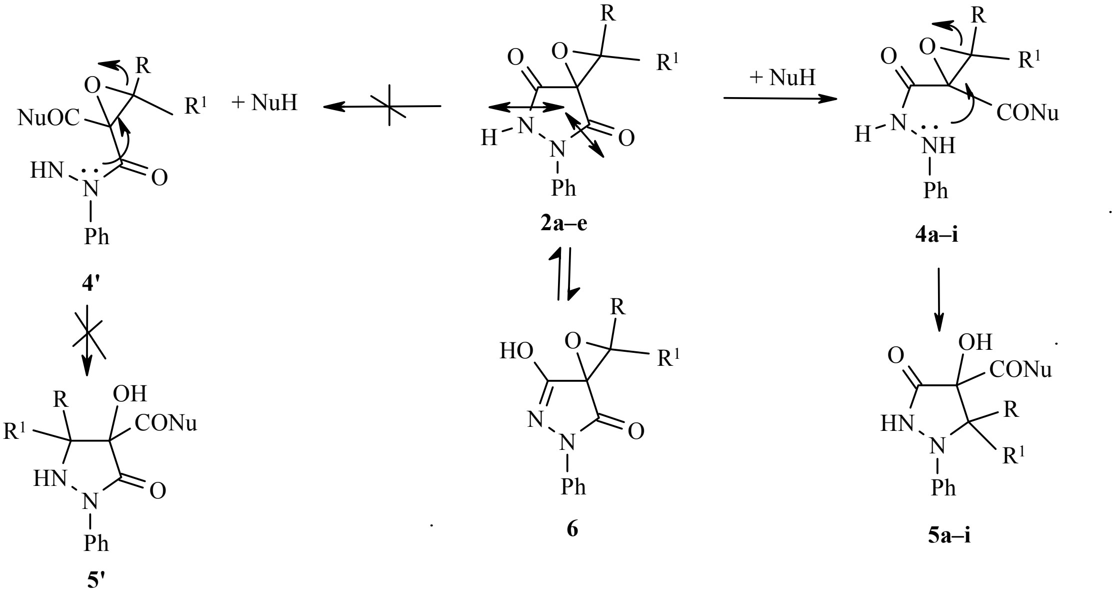
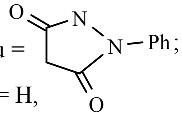
The structure of compounds **2a-c** was elucidated using elemental analysis, mass spectrometry, IR and, particularly, NMR spectroscopy. The characteristic structural feature in the ^{1}H NMR analysis of **2c-h** is the oxirane proton found at δ values 4.5-5.2 ppm according to the type of the adjacent aromatic substituent [15, 16]. Likewise, ^{1}H NMR spectra of compounds **2c-h** indicated the presence of two isomers in equal amounts as shown by the existence of two oxirane proton signals. This proves the formation of the diazaspiro derivatives **2c-h** as mixtures of diastereomers although according to the literature [17] the epoxidation of α,β-unsaturated ketones with alkaline hydrogen peroxide is diastereoselective.

The pairs of racemic diastereomers **2c-h** were separated using the HPLC technique, and further investigations are in progress.

Derivatives **2a-h** are expected to be reactive intermediates due to the highly strained spirooxirane ring. The present investigation will cover the reactivity of **2a-e** with nucleophilic reagents, including nitrogen, oxygen, and carbon nucleophiles. The reaction products depend on the spirooxirane derivatives used. Spiro derivatives **2a**,**b** without aromatic substituents on the oxirane ring react with nucleophilic reagents, forming the corresponding adducts. Thus 2,2-dimethyl-5-phenyl-1-oxa-5,6-diazaspiro[2.4]heptane-4,7-dione (**2a**) and 2-phenyl-12-oxa-2,3-diazadispiro[4.0.5.1]dodecane-1,4-dione (**2b**) can react with different nucleophiles in a unique fashion *via* ring transformation to give either 5,5-dialkyl-4-hydroxy-3-oxo-1-phenylpyrazolidine-4-carboxylic acid derivatives **5a-f** or their 3,3-dialkyl isomers **5'**. Such ring transformation may occur *via* the intermediates **4** or **4'** following the proposed reaction mechanism (Scheme 2). Intermediates similar to **4** have been isolated previously [18].

Scheme 2



2a, 5a–d R = R¹ = Me, **5 a** Nu = $HNNH_2$, **b** Nu = HNNHPh, **c** Nu = OMe, **d** Nu = ;

2b, 5e,f R = R¹ = $(CH_2)_5$, **5 e** Nu = $HNNH_2$, **f** Nu = HNNHPh; **2c–e, 5g–i** R = H,

2c, 5g R¹ = Ph, **2d, 5h** R¹ = 4-MeC_6H_4, **2e, 5i** R¹ = 2-$MeOC_6H_4$, **5g–i** Nu = $HNNH_2$

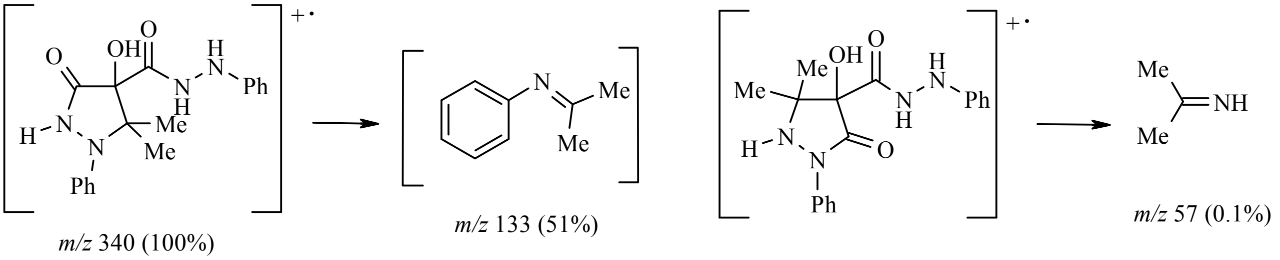
The assigned structures of the products **5a–i** are inferred from elemental analysis and spectral data using also comparison with similar compounds [16, 19]. The ^{1}H NMR spectrum of **5b** indicates a singlet at 1.16 and 1.27 ppm, a deuterium-exchangeable signal at 5.66 (OH), and broad singlets at 6.69 (NH) and 9.99 ppm (amidic NH). The 10 aromatic protons are seen as a group of multiplets at 6.7-7.8 ppm.

The ^{13}C NMR spectrum of compound **5b** conforms to the proposed structure. The ^{15}N NMR spectrum of compound **5b** shows two signals at 63.09 and at 130.86 ppm, which correspond to one tertiary and three secondary nitrogens.

The IR absorption spectrum of **5b** indicates the presence of the following characteristic absorption bands: 3310 (NH), 1680 and 1640 cm^{-1} (C=O).

Mass spectrometric analysis of compound **5b** adds additional confirmation for the suggested structure. The molecular ion represents the most abundant peak, which reflects its high stability under electron impact. The fragmentation pathway of the molecular ion (*m/z* 340) indicates the presence of an ion at *m/z* 133 $[C_6H_5N{=}C(CH_3)_2]^+$ with high relative abundance (51%). The appearance of this stable ion (acetone anil ion) and the very low abundance (0.1%) of the ion at *m/z* 57 ($(CH_3)_2C{=}NH$, acetoneimine) can be considered as evidence for the suggested structure **5b** (Scheme 3).

Scheme 3



m/z 340 (100%)
5b

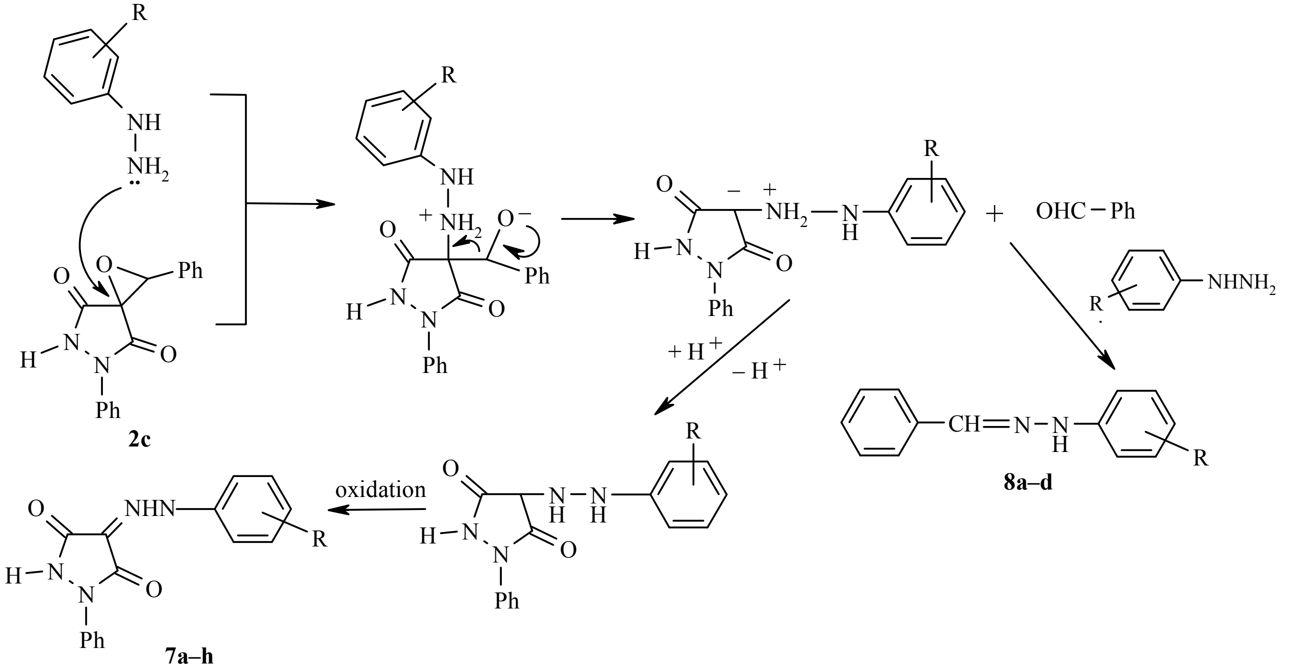
m/z 133 (51%)

m/z 340 (100%)
5'b

m/z 57 (0.1%)

The resolution of **5b** to the corresponding diastereomers and optically active isomers is under investigation.

Scheme 4



2c

8a–d

7a–h

7 a R = H, **b** R = 4-OMe, **c** R = 2-Cl, **d** R = 3-Cl, **e** R = 4-Cl, **f** R = 3-Br, **g** R = 2-NO_2, **h** R = 3-NO_2; **8 a** R = H, **b** R = 2-NO_2, **c** R = 3-NO_2, **d** R = 3-Br

5-Phenyl-1-oxa-5,6-diazaspiro[2.4]heptane-4,7-dione derivatives **2c-e** with an aromatic group on the oxirane ring reacted with hydrazine hydrate with ring transformation to give the 1,5-diarylpyrazolidin-3-one derivatives **5g-i** as expected. With the use of phenylhydrazine or substituted phenylhydrazine with oxiranes **2c-e** having aryl substituent on the oxirane ring, no ring transformation reaction occurred. Starting with **2c** as an example, from its reaction with phenylhydrazine derivatives, 4-arylhydrazono-1-phenyl-3,5-pyrazolidinediones **7a-h** were isolated, as well as benzaldehyde phenylhydrazone derivatives **8a-d** with the characteristics reported in the literature [20]. The mechanism for the formation of **7** and **8** is proposed in Scheme 4.

EXPERIMENTAL

Melting points were measured with a Gallenkamp electronic melting point apparatus and are uncorrected. Elemental analyses were performed on an Elementar Vario EI apparatus. Infrared spectra were recorded with a Shimadzu 470 infrared spectrophotometer (KBr wafer technique). ^{1}H NMR, ^{13}C NMR, and ^{15}N NMR spectra were recorded on a Bruker AMX 500 NMR spectrometer (400, 100, and 50.68 MHz, respectively) in DMSO-d_6 (for compounds **2b,c** – $CDCl_3$) using TMS as the internal standard for ^{1}H and ^{13}C. Chemical shifts for ^{15}N are reported with respect to the external standard of saturated $^{15}NH_4Cl$ in D_2O. Chemical shifts are reported in ppm (δ scale). Mass spectra were recorded on Jeol JMS 600 spectrometer (FAB for compound **5b**, 70 eV EI for all other compounds). HPLC analyses were performed on a Merck Hitachi 655 A-11 liquid chromatograph using an RP-C18 column, 655A variable wavelength UV monitor, and D-2000 integrator.

Synthesis of 5-Phenyl-1-oxa-5,6-diazaspiro[2.4]heptane-4,7-dione Derivatives 2 (General Method). The 4-alkylidene(arylidene)-1-phenyl-3,5-pyrazolidinediones **1a-h** [1-4] (4 mmol) were suspended in acetonitrile (25 ml), and aqueous hydrogen peroxide solution (30%, 10 ml) was added to the stirred suspension followed by aqueous sodium hydroxide solution (10%, 1-3 ml).

A. As soon as the color of the original 4-alkylidene(arylidene)-1-phenyl-3,5-pyrazolidinedione disappeared, the reaction mixture was filtered off. The resulting filtrate was diluted with water and neutralized with oxalic acid (5%) to give a precipitate which was collected, crystallized from the proper solvent, and identified as the corresponding products **2a-h.**

B. In the case of the soluble 5-phenyl-1-oxa-5,6-diazaspiro[2.4]heptane-4,7-dione, the reaction product was isolated by extraction twice with diethyl ether. The ether layer was dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure. The residue was purified by crystallization from the proper solvent.

2,2-Dimethyl-5-phenyl-1-oxa-5,6-diazaspiro[2.4]heptane-4,7-dione (2a). White amorphous solid from ether, yield 75%; mp 150-152°C. IR spectrum, ν, cm^{-1}: 3190 (NH), 3050 (aromatic CH), 2900 and 2850 (aliphatic CH), 1730 (C=O), 1700 (C=O), 1110 (st. vib. C–O), 900 (epoxide ring). ^{1}H NMR spectrum, δ, ppm: 1.07 (3H, s, CH_3); 1.72 (3H, s, CH_3); 7.25 (1H, m, *p*-H Ar); 7.41 (2H, m, *m*-H Ar); 7.61 (1H, br. s, NH); 7.62 (2H, m, *o*-H Ar). ^{13}C NMR spectrum, δ, ppm: 18.56 (CH_3), 18.98 (CH_3), 59.88 (C-2), 71.57 (C-3), 135.52, 118.68, 129.40, and 126.33 (C_6H_5), 161.68 (C=O), 168.83 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 232 $[M]^+$ (31), 231 (1), 217 (2), 216 (5), 204 (2), 176 (7), 58 (8), 28 (100). Found, %: C 62.22; H 5.21; N 12.12. $C_{12}H_{12}N_2O_3$. Calculated, %: C 62.01; H 5.17; N 12.06.

2-Phenyl-12-oxa-2,3-diazadispiro[4.0.5.1]dodecane-1,4-dione (2b). Pale-yellow amorphous solid from $CHCl_3$–petroleum ether, 1:1, yield 53.3%; mp 185°C. IR spectrum, ν, cm^{-1}: 3180 (NH), 3050 (aromatic CH), 2900 and 2850 (aliphatic CH), 1730 (C=O), 1700 (C=O), 1110 (st. vib. C–O), 890 (epoxide ring). ^{1}H NMR spectrum, δ, ppm: 1.39 (4H, m, 8,10-CH_2); 1.80 (2H, m, 9-CH_2); 2.11 (4H, m, 7,11-CH_2); 7.26 (2H, m, *o*-H Ar); 7.36 (1H, br. s, NH); 7.47 (1H, m, *p*-H Ar); 7.63 (2H, m, *m*-H Ar). ^{13}C NMR spectrum, δ, ppm: 25.14, 25.58, 28.16, and 28.65 (cyclohexane ring), 59.95 (C-7), 118.71, 126.35, 129.47, 135.73 (C_6H_5), 161.66 (C=O), 168.96 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 272 [M]$^+$ (19), 271 (100), 256 (0.4), 244 (10); 176 (1), 108 (46). Found, %: C 66.01; H 5.88; N 10.21. $C_{15}H_{16}N_2O_3$. Calculated, %: C 66.11; H 5.88; N 10.28.

2,5-Diphenyl-1-oxa-5,6-diazaspiro[2.4]heptane-4,7-dione (2c). Pale-yellow amorphous solid from benzene, yield 62.9%; mp 160°C. IR spectrum, ν, cm^{-1}: 3150 (NH), 3050 (aromatic CH), 2850 (aliphatic CH), 1740 (C=O), 1700 (C=O), 1105 (st. vib. C–O), 895 (epoxide ring). ^{1}H NMR spectrum, δ, ppm: 4.63 and 4.66 (1H, s, oxirane); 7.34 (2H, m, *p*-H Ar); 7.58 (2H, m, *o*-H Ar); 7.62 (4H, m, *m*-H Ar); 7.85 (2H, m, *o*-H Ar); 8.01 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 58.35 (C-2), 67.93 (C-3), 127.88, 128.84, 129.10, 129.80, 130.11, 136.23 and 144.51 (C_6H_5), 166.05 (C=O), 166.60 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 280 [M]$^+$ (99), 279 (2), 265 (1), 252 (2), 251 (7), 247 (3), 195 (141), 106 (19), 56 (100). Found, %: C 68.61; H 4.31; N 9.89. $C_{16}H_{12}N_2O_3$. Calculated, %: C 68.51; H 4.28; N 9.92.

Quantitative HPLC Analysis of 5-Phenyl-1-oxa-5,6-diazaspiro[2.4]heptane-4,7-dione Derivatives 2. A highly pure sample of **2c** was dissolved in acetonitrile to give 1×10^{-3} M solution. Then 20 μl of that solution was injected on an RP-C_{18} column, the flow rate was adjusted to 1.2 ml/min using a acetonitrile–water, 70:30, as eluent, and the product detection was done using UV-detector at λ 254 nm. Two isomers were separated in the ratio 53:47 with retention times 3.02 and 5.82 min, respectively.

2-(4-Methylphenyl)-5-phenyl-1-oxa-5,6-diazaspiro[2.4]heptane-4,7-dione (2d). Pale-yellow granular solid from ethanol, yield 80.2%; mp 130°C. IR spectrum, ν, cm^{-1}: 3150 (NH), 3050 (aromatic CH), 2900 and 2850 (aliphatic CH), 1720 (C=O), 1700 (amidic C=O), 1110 (st. vib. C–O), 905 (epoxide ring). ^{1}H NMR spectrum, δ, ppm: 2.31 (3H, s, CH_3); 4.65 and 4.71 (1H, s, CH oxirane); 7.17 (2H, m, *o*-H Ar); 7.19 (2H, m, *m*-H Ar); 7.49 (2H, m, *o*-H Ph); 7.51 (2H, m, *m*-H Ph); 7.55 (1H, s, NH); 7.91 (1H, m, *p*-H Ph). ^{13}C NMR spectrum, δ, ppm: 20.81 (CH_3), 56.06 and 64.83 (C-2), 75.07 (C-3), 118.78, 125.16, 128.87 and 136.30 (C_6H_5), 127.89, 128.35, 128.49, and 129.05 (4-MeC_6H_4), 164.22 (C=O), 166.65 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 294 [M]$^+$ (43.9), 293 (4), 278 (6); 279 (3), 266 (2), 265 (4), 209 (56), 120 (9), 91 (100). Found, %: C 69.25; H 4.70; N 9.55. $C_{17}H_{14}N_2O_3$. Calculated, %: C 69.32; H 4.76; N 9.51.

2-(2-Methoxyphenyl)-5-phenyl-1-oxa-5,6-diazaspiro[2.4]heptane-4,7-dione (2e). Pale-yellow granular solid from benzene–ethanol, 8:2, 85.4%; mp 160°C. IR spectrum, ν, cm^{-1}: 3400 (NH), 3190 (aromatic CH), 2900 and 2850 (aliphatic CH), 1740 (C=O), 1710 (C=O), 1110, 900 (epoxide ring). ^{1}H NMR spectrum, δ, ppm: 3.51 (3H, s, OCH_3); 4.65 and 4.69 (1H, s, CH oxirane); 6.99 (1H, m, *m*-H Ar); 7.03 (1H; m, *o*-H Ar); 7.19 (1H, m, *m*-H Ar); 7.35 (1H, m, *p*-H Ar); 7.41 (2H, m, *o*-H Ph); 7.48 (1H, m, *p*-H Ph); 7.57 (2H, m, *m*-H Ph); 7.65 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 55.64 (OCH_3), 71.14 and 75.26 (C-2), 78.55 (C-3), 121.52, 126.52, 128.76 and 139.44 (C_6H_5), 111.73, 121.05, 124.23, 126.85, 129.69, and 157.72 (2-$CH_3OC_6H_4$), 166.98 (C=O), 168.22 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 310 [M]$^+$ (2), 309 (2), 295 (5.3), 294 (21.3), 282 (11.1), 281 (1.3), 136 (10.8). Found, %: C 65.81; H 4.61; N 9.03. $C_{17}H_{14}N_2O_4$. Calculated, %: C 65.74; H 4.51; N 9.02.

2-(4-Chlorophenyl)-5-phenyl-1-oxa-5,6-diazaspiro[2.4]heptane-4,7-dione (2f). White granular solid from benzene–ethanol, 7:3, yield 60.1%; mp 187°C. IR spectrum, ν, cm^{-1}: 3250 (NH), 3050 (aromatic CH), 2950 and 2900 (aliphatic CH), 1670 (C–O), 1180, 900 (epoxide ring). ^{1}H NMR spectrum, δ, ppm: 4.73 and 4.79 (1H, s, CH oxirane); 7.21 (2H, m, *o*-H Ar); 7.25 (2H, m, *m*-H Ar); 7.37 (2H, m, *o*-H Ph); 7.42 (1H, m, *p*-H Ar); 7.56 (2H, m, *m*-H Ph); 7.68 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 58.05 and 58.39 (C-2), 65.41 (C-3), 118.91, 125.41, 129.67 and 136.30 (C_6H_5), 128.32, 131.18, 133.71 and 160.41 (4-ClC_6H_4), 161.41 (C=O), 164.90 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 314 [M]$^+$ (6), 313 (6), 315 (2), 298 (6), 300 (2), 299 (7), 301 (0.4), 286 (1), 288 (1), 285 (2), 287 (5), 229 (11), 231 (2), 140 (3), 142 (0.4), 111 (100). Found, %: C 61.15; H 3.52; N 8.92. $C_{16}H_{11}ClN_2O_3$. Calculated, %: C 61.01; H 3.49; N 8.89.

2-(2-Nitrophenyl)-5-phenyl-1-oxa-5,6-diazaspiro[2.4]heptane-4,7-dione (2g). Pale-yellow granular solid from benzene–ethanol, 8:2, yield 63.39%; mp 185-187°C. IR spectrum, ν, cm^{-1}: 3190 (NH), 3080 (aromatic CH), 2900 and 2850 (aliphatic CH), 1740 (C=O), 1705 (C=O), 1150, 915 (epoxide ring). ^{1}H NMR spectrum, δ, ppm: 5.13 and 5.17 (1H, s, CH oxirane); 7.21 (2H, m, *o*-H Ph); 7.36 (1H, m, *p*-H Ph); 7.41 (1H, m, *o*-H Ar); 7.66 (1H, m, *p*-H Ar); 7.72 (2H, m, *m*-H Ph); 8.19 (2H, m, *m*-H Ar); 8.21 (1H, s, NH). ^{13}C NMR spectrum, NMR spectrum, δ, ppm: 58.17 and 63.57 (C-2), 64.05 (C-3), 118.88, 124.41, 125.52, 128.97, 129.14, 130.18, 134.26, 136.28 and 146.58 (Ar), 160.23 (C=O), 161.42 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 325 $[M]^+$ (42), 324 (1), 309 (10), 310 (4), 297 (2), 296 (2), 240 (3), 151 (18), 46 (100). Found, %: C 59.20; H 3.22; N 12.23. $C_{16}H_{11}N_3O_5$. Calculated, %: C 59.03; H 3.38; N 12.19.

2-(4-Nitrophenyl)-5-phenyl-1-oxa-5,6-diazaspiro[2.4]heptane-4,7-dione (2h). Yellow granular solid from benzene–ethanol, 7:3, yield 47.6%; mp 215°C. IR spectrum, ν, cm^{-1}: 3200 (NH), 3050 (aromatic CH), 2900 and 2850 (aliphatic CH), 1110, 895 (epoxide ring). ^{1}H NMR spectrum, δ, ppm: 4.86 and 4.91 (1H, s, CH oxirane); 7.21 (1H, m, *p*-H Ph); 7.36 (2H, m, *m*-H Ph); 7.57 (2H, m, *o*-H Ph); 7.67 (1H, s, NH); 7.87 (2H, m, *o*-H Ar); 8.23 (2H, m, *m*-H Ar). ^{13}C NMR spectrum, δ, ppm: 58.24 and 64.02 (C-2), 64.58 (C-3), 118.79, 125.21, 129.29, 136.52, and 138.51 (C_6H_5), 122.63, 128.97, 136.52, 147.66 (4-$NO_2C_6H_4$), 160.30 (C=O), 164.08 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 325 $[M]^+$ (70.4), 310 (4.9), 297 (3.9), 296 (0.7), 240 (4.9), 151 (100). Found, %: C 59.05, H 3.41; N 12.95. $C_{16}H_{11}N_3O_5$. Calculated, %: C 59.04, H 3.38; N 12.91.

4-Hydroxy-5,5-dimethyl-3-oxo-1-phenylpyrazolidine-4-carbohydrazide (5a). White flakes from ethanol, yield 70.4%; mp 225°C. IR spectrum, ν, cm^{-1}: 3400 and 3300 (NH_2), 3200 (NH), 3050 (aromatic CH), 2950 (aliphatic CH), 1680 (C=O), 1620 (C=O) 1590 (bending vib. NH). ^{1}H NMR spectrum, δ, ppm: 1.08 (3H, s, CH_3); 1.15 (3H, s, CH_3); 4.39 (2H, s, $NHN\underline{H}_2$); 5.63 (1H, s, OH); 6.65 (1H, m, $N\underline{H}NH_2$); 7.12 (1H, m, *p*-H Ph); 7.37 (2H, m, *m*-H Ph); 7.80 (2H, m, *o*-H Ph); 9.24 (1H, s, NHC=O). ^{13}C NMR spectrum, δ, ppm: 21.70 (CH_3), 24.95 (CH_3), 62.21 (C-5), 83.73 (C-4), 118.01, 124.18, 128.60, and 139.21 (C_6H_5), 167.75 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 264 $[M]^+$ (100), 263 (94), 262 (21), 250 (3), 249 (11), 247 (12), 236 (2), 234 (12), 233 (2), 207 (20), 205 (85), 187 (4), 178 (9), 176 (74), 175 (7), 130 (17). Found, %: C 54.51; H 6.12; N 21.22. $C_{12}H_{16}N_4O_3$. Calculated, %: C 54.49; H 6.05; N 21.19.

4-Hydroxy-5,5-dimethyl-3-oxo-N',1-diphenylpyrazolidine-4-carbohydrazide (5b). Pale-yellow flakes from ethanol, yield 68.3%; mp 185°C. IR spectrum, ν, cm^{-1}: 3310 (amidic st. vib. NH), 3050 (aromatic CH), 2900 and 2950 (aliphatic CH), 1680 (C=O), 1640 (C=O), 1590 (amidic bending vib. NH). ^{1}H NMR spectrum, δ, ppm: 1.16 (3H, s, CH_3); 1.27 (3H, s, CH_3); 5.66 (1H, s, OH); 6.69 (2H, s, NHNH); 6.71 (1H, m, *p*-H Ar); 6.80 (4H, m, *o*-H Ar); 7.14 (1H, m, *p*-H Ar); 7.37 (2H, m, *m*-H Ar); 7.81 (2H, m, *m*-H Ar); 9.99 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 19.74 (CH_3), 21.96 (CH_3), 62.45 (C-5), 83.96 (C-4), 112.52, 118.00, 128.68, and 139.20 (C_6H_5), 118.66, 124.16, 128.60, 149.22 (C_6H_5), 169.64 (C=O), 170.29 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 340 $[M]^+$ (100), 339 (43), 338 (8), 326 (0.2), 249 (2), 233 (2), 206 (68), 205 (3) 176 (5), 175 (4), 148 (66), 134 (12), 133 (51). Found, %: C 63.48; H 5.91; N 16.42. $C_{18}H_{20}N_4O_3$. Calculated, %: C 63.46; H 5.88; N 16.45.

4-Hydroxy-3-oxo-1-phenyl-1,2-diazaspiro[4.5]decane-4-carbohydrazide (5e). White flakes from ethanol, yield 71.7%; mp 215°C. IR spectrum, ν, cm^{-1}: 4300 and 3300 (NH_2), 3200 (amidic st. vib. NH), 3050 (aromatic CH), 2900 and 2850 (aliphatic CH), 1680 (C=O), 1660 (C=O), 1630 (amidic bending vib. NH). ^{1}H NMR spectrum, δ, ppm: 1.37, 1.42 and 1.67 (10H, m, $(CH_2)_5$); 4.35 (2H, s, $NHN\underline{H}_2$); 5.47 (1H, s, OH); 7.11, 7.64 and 7.37 (6H, m, Ar and $N\underline{H}NH_2$); 9.17 (1H, s, NHC=O). ^{13}C NMR spectrum, δ, ppm: 21.32, 25.31, 27.89 (cyclohexane ring), 63.80 (C-5), 84.22 (C-4), 117.83, 123.92, 128.62, and 139.46 (C_6H_5), 167.53 (C=O), 170.71 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 303 $[M-H]^+$ (15.1), 188 (7), 179 (17), 170 (12), 145 (11), 117 (16), 103 (20), 75 (21), 46 (100). Found, %: C 59.22; H 6.67; N 18.41. $C_{15}H_{20}N_4O_3$. Calculated, %: C 59.14; H 6.57; N 18.39.

4-Hydroxy-3-oxo-N',1-diphenyl-1,2-diazaspiro[4.5]decane-4-carbohydrazide (5f). Dark-yellow flakes from ethanol, yield 71.6%; mp 139°C. IR spectrum, ν, cm^{-1}: 3320 (amidic st. vib. NH), 3050 (aromatic CH), 2950 and 2850 (aliphatic CH), 1680 (C=O), 1640 (C=O), 1590 (amidic bending vib. NH). ^{1}H NMR spectrum, δ, ppm: 1.38, 1.49, and 1.66 (10H, m, $(CH_2)_5$); 5.48 (1H, s, OH); 6.69, 6.81, 7.12, 7.37, 7.67, 7.77, and 7.84 (12H, m, 10 H Ar and 2 NH); 9.95 (1H, s, NHC=O). ^{13}C NMR spectrum, δ, ppm: 21.38, 25.31, 27.87 (cyclohexane ring), 64.02 (C-5), 84.56 (C-4), 117.91, 118.59, 123.98, 125.44, 128.50, 128.98, 139.39, 149.22 (C_6H_5), 169.33 (C=O), 170.44 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 379 $[M-H]^+$ (17), 231 (6), 203 (8), 189 (14), 188 (27), 161 (5), 28 (100). Found, %: C 66.31; H 6.26; N 14.33. $C_{22}H_{24}N_4O_3$. Calculated, %: C 67.27; H 6.12; N 14.27.

Reaction of 2,2-Dimethyl-5-phenyl-1-oxa-5,6-diazaspiro[2.4]heptane-4,7-dione (2a) with Sodium Methoxide in Absolute Methanol (Oxygen Nucleophile). A mixture of equimolar amounts (0.1 mmol) of compound **2a** and sodium methoxide in the presence of absolute methanol as a solvent was refluxed for 4 h. After filtration, the resulting filtrate was evaporated under reduced pressure till dryness. The resulting residue was neutralized by dilute HCl to give a precipitate that was collected and crystallized from chloroform–petroleum ether, 3:7, and identified as methyl 4-hydroxy-5,5-dimethyl-3-oxo-1-phenyl-pyrazolidine-4-carboxylate (**5c**) in the form of pale-yellow flakes, yield 70.4%; mp 118-120°C. IR spectrum, ν, cm^{-1}: 3190 (amidic st. vib. NH), 3050 (aromatic CH), 2900 and 2850 (aliphatic CH), 1730 (C=O), 1700 (C=O), 1580 (amidic bending vib. NH). ^1H NMR spectrum, δ, ppm: 1.61, 1.60 (6H; s, $C(CH_3)_2$); 3.72 (3H, s, $COOCH_3$); 7.22, 7.40, 7.66, 7.79 and 7.81 (7H, m, H Ar, NH, and OH). ^{13}C NMR spectrum, δ, ppm: 18.05 (CH_3), 18.54 (CH_3), 52.39 ($COO\underline{C}H_3$), 69.87 (C-5), 84.07 (C-4), 118.88, 123.37, 128.59, 136.28 (C_6H_5), 169.21 (C=O), 170.05 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 264 $[M]^+$ (2), 263 (9), 262 (2), 250 (10), 249 (1), 247 (1), 234 (1), 233 (1), 207 (2), 205 (34), 187 (7), 175 (4), 148 (14), 130 (3), 46 (100). Found, %: C 57.09; H 5.99; N 10.68. $C_{13}H_{16}N_2O_4$. Calculated, %: C 59.03; H 6.05; N 10.59.

Reaction of 2,2-Dimethyl-5-phenyl-1-oxa-5,6-diazaspiro[2.4]heptane-4,7-dione (2a) with the Sodium Salt of 1-Phenyl-3,5-pyrazolidinedione (Carbon Nucleophile). A mixture of equimolar amounts (0.1 mmol) of compound **2a** (0.467 g, 2.00 mmol), 1-phenyl-3,5-pyrazolidinedione (0.352 g, 2.00 mol), and metallic sodium (0.046 g, 2.0 mmol) in absolute ethanol as a solvent was refluxed for 6 h. After cooling, the reaction mixture was diluted and acidified by dilute HC1 to give a precipitate that was collected and crystallized from ethanol, and identified as 1-[(4-hydroxy-5,5-dimethyl-3-oxo-1-phenylpyrazolidin-4-yl)carbonyl]-2-phenylpyrazolidine-3,5-dione (**5d**) in the form of a pale-yellow granular solid from ethanol, yield 56.9%; mp 210°C. IR spectrum, ν, cm^{-1}: 3210 (amidic st. vib. NH), 3050 (aromatic CH), 2900 (aliphatic CH), 1740 (C=O), 1700 (C=O), 1589 (bending vib. NH). ^1H NMR spectrum, δ, ppm : 2.67 (6H, s, $2CH_3$); 5.96 (1H, s, OH); 7.51 (13H, m, H Ar, 2 NH and OH). ^{13}C NMR spectrum, δ, ppm: 16.47 (CH_3), 53.23 (C-5), 111.82 (C-4), 118.21, 122.97, 129.03, 144.30 (C_6H_5), 119.56, 121.58, 128.85, 146.99 (C_6H_5), 160.55 (C=O), 170.34 (C=O), 174.42 (C=O), 194.46 (C=O). FAB mass spectrum, *m/z* (I_{rel}, %): 408 $[M]^+$ (2). Found, %: C 61.67; H 4.85; N 13.66. $C_{21}H_{20}N_4O_5$. Calculated, %: C 61.71; H 4.89; N 13.71.

Reaction of 5-Phenyl-1-oxa-5,6-diazaspiro[2.4]heptane-4,7-dione Derivatives 2c-e with Hydrazine Hydrate (Nitrogen Nucleophiles) (General Method). A mixture of equimolar amounts (0.1 mmol) of compounds **2c–e** and hydrazine hydrate in absolute ethanol was refluxed for 4 h. After cooling, the precipitate was collected, crystallized from the proper solvent, and identified as 5-aryl-4-hydroxy-3-oxo-1-phenyl-pyrazolidine-4-carboxylic acid hydrazides **5g-i**. The results are summarized as follows.

4-Hydroxy-3-oxo-1,5-diphenylpyrazolidine-4-carbohydrazide (5g). White granular solid from ethanol, yield 71.8 %; mp 300°C. IR spectrum, ν, cm^{-1}: 3350 and 3250 (NH_2), 3050 (aromatic CH), 2900 and 2850 (aliphatic CH), 1740 (C=O), 1640 (amidic C=O), 1590 (amidic bending vib. NH). ^1H NMR spectrum, δ, ppm : 4.65 (1H, s, H-5 pyrazolone); 4.59 (1H, s, OH); 5.36 (2H, s, NH_2); 6.06, 6.55, 6.86, and 7.39 (10H, m, H Ar); 9.44 (1H, s, NH); 9.93 (1H, s, NHC=O). ^{13}C NMR spectrum, δ, ppm: 70.44 (C-5), 80.69 (C-4), 112.01, 118.08, 124.60, 126.31, 128.30, 134.76, and 148.59 (C_6H_5), 168.21 (C=O), 173.65 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 312 $[M]^+$ (38), 311 (0.4), 310 (0.3), 298 (1), 297 (2), 295 (1), 253 (6), 235 (2), 134 (6), 28 (100). Found, %: C 61.59; H 5.15; N 17.85. $C_{16}H_{16}N_4O_3$. Calculated, %: C 61.48; H 5.12; N 17.93.

4-Hydroxy-3-(4-methylphenyl)-5-oxo-1-phenylpyrazolidine-4-carbohydrazide (5h). White granular solid from ethanol, yield 72.7%; mp 230°C. IR spectrum, ν, cm^{-1}: 3390 and 3220 (NH_2), 3050 (aromatic CH), 2900 and 2850 (aliphatic CH), 1700 (C=O), 1650 (C=O) 1590 (amidic bending vib. NH). ^1H NMR spectrum, δ, ppm: 2.33 (3H, s, CH_3); 5.18 (1H, s, H-5 pyrazolone); 5.21 (1H, s, OH); 5.06 (2H, s, NH_2); 6.60 (1H, s, NH); 7.56, 7.93, 7.43, 7.17 and 7.20 (9H, m, H Ar); 11.35 (1H, s, NHC=O). ^{13}C NMR spectrum, δ, ppm: 20.73 (CH_3), 65.12 (C-5), 82.27 (C-4), 112.22, 118.28, 129.47, 149.18 (C_6H_5), 127.17, 128.76, 137.18, 139.71 (4-$CH_3C_6H_4$), 165.69 (C=O), 168.29 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 326 $[M]^+$ (15), 325 (76), 324 (1), 312 (0.4), 309 (3), 295 (3), 267 (4), 235 (2), 234 (2), 209 (17), 134 (34), 28 (100). Found, %: C 62.51; H 5.61; N 17.40. $C_{12}H_{18}N_4O_3$. Calculated, %: C 62.60; H 5.61; N 17.21.

4-Hydroxy-3-(2-methoxylphenyl)-5-oxo-1-phenylpyrazolidine-4-carbohydrazide (5i). Orange granular solid from ethanol, yield 80.9%; mp 175°C. IR spectrum, ν, cm^{-1}: 3400 and 3300 (NH_2), 3040 (aromatic CH), 2900 and 2850 (aliphatic CH), 1680 (C=O), 1590 (amidic bending vib. NH). ^{1}H NMR spectrum, δ, ppm: 3.70 (3H, s, OCH_3); 5.22 (1H, s, 5-H pyrazolone); 5.24 (1H, s, OH); 6.29 (2H, s, $NHN\underline{H_2}$); 6.58 (1H, s, $N\underline{H}NH_2$); 6.88, 6.90, 6.96, 7.26, 7.42, 7.63, and 7.70 (9H, m, H Ar); 8.93 (1H, s, NHC=O). ^{13}C NMR spectrum, δ, ppm: 55.54 (OCH_3), 81.35 (C-4), 110.72, 118.30, 128.79, 138.52 (C_6H_5), 117.87, 128.14, 128.79, 128.90, 133.33, 155.82 (2-$MeOC_6H_4$), 128.79 (C-5), 157.25 (C=O), 168.31 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 342 $[M]^+$ (1), 341 (3), 340 (1), 327 (0.4), 325 (2), 311 (1), 283 (4), 235 (1), 234 (3), 225 (64), 134 (29), 46 (100). Found, %: C 59.49; H 5.22; N 16.46. $C_{17}H_{18}N_4O_4$. Calculated, %: C 59.58; H 5.26; N 16.36.

Reactions of 2,5-Diphenyl-1-oxa-5,6-diazaspiro[2.4]heptane-4,7-dione (2c) with Phenylhydrazine and Substituted Phenylhydrazines (General Method). A mixture of equimolar amounts (0.1 mmol) of **2c** and phenylhydrazine or substituted phenylhydrazine in absolute ethanol was refluxed for 4 h. After cooling, a precipitate was formed, which was collected, crystallized from the proper solvent, and identified as 4-arylhydrazono-1-phenyl-3,5-pyrazolidinediones **7a-c** [17]. The filtrate was evaporated under reduced pressure, and the remaining residue was crystallized from the proper solvent. The product was identified as the corresponding benzaldehyde arylhydrazones **8a-d**.

1-Phenyl-4-(2-phenylhydrazinylidene)pyrazolidine-3,5-dione (7a). Orange flakes from ethanol, yield 62%; mp 232–233 °C (232°C lit. [17]). IR spectrum, ν, cm^{-1}: 3200 (NH), 3040 (aromatic CH), 2900 and 2850 (aliphatic CH), 1710 (C=O), 1640 (C=O), 1590 (N=N), 1550 (C=N). Mass spectrum, *m/z* (I_{rel}, %): 280 $[M]^+$ (16), 279 (100), 119 (2), 106 (10), 92 (49). Found, %: C 64.31; H 4.30; N 19.68. $C_{15}H_{12}N_4O_2$. Calculated, %: C 64.22; H 4.28; N 19.98.

Benzaldehyde Phenylhydrazone (8a). Pale-yellow needles from cyclohexane, yield 57.1%; mp 158–160 °C, mp of a mixture with authentic sample 158-160°C. IR spectrum, ν, cm^{-1}: 3285 (NH), 3020 (aromatic CH), 1585 (C=N). Found, %: C 79.52; H 5.98, N 14.35. $C_{13}H_{12}N_2$. Calculated, %: C 79.59; H 6.12; N 14.28.

4-[2-(4-Methoxyphenyl)hydrazinylidene]-1-phenylpyrazolidine-3,5-dione (7b). Orange flakes from ethanol, yield 54.3%; mp 238-240°C. IR spectrum, ν, cm^{-1}: 3150 (NH), 3030 (aromatic CH), 2850 (aliphatic CH), 1680 (C=O), 1650 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 310 $[M]^+$ (21), 309 (100), 279 (2), 135 (2), 122 (38). Found, %: C 62.01; H 4.45; N 17.99. $C_{16}H_{14}N_4O_3$. Calculated, %: C 61.88; H 4.52; N 18.11.

4-[2-(2-Chlorophenyl)hydrazinylidene]-1-phenylpyrazolidine-3,5-dione (7c). Brown granular solid from ethanol, yield 50.9%; mp 238°C. IR spectrum, ν, cm^{-1}: 3200 (NH), 3050 (aromatic CH), 2950 (aliphatic CH), 1690 (C=O), 1660 (C=O), 1580 (N=N). Mass spectrum, *m/z* (I_{rel}, %): 316 (4), 314 (14), 313 (46), 128 (15), 28 (100). Found, %: C 57.45, H 3.52 N 17.85. $C_{15}H_{11}N_4O_2$. Calculated, %: C 57.32, H 3.50, N 17.83.

4-[2-(3-Chlorophenyl)hydrazinylidene]-1-phenylpyrazolidine-3,5-dione (7d). Orange granular solid from ethanol, yield 43.2%; mp 143-145°C. IR spectrum, ν, cm^{-1}: 3150 (NH), 3050 (aromatic CH), 2900 and 2850 (aliphatic CH), 1690 (C=O), 1660 (C=O), 1560 (N=N). Mass spectrum, *m/z* (I_{rel}, %): 315 (14), 313 (55), 175 (8), 128 (7), 126 (45), 106 (7), 103 (15), 91 (13), 77 (7), 56 (100). Found, %: C 57.28; H 3.49; N 17.85. $C_{15}H_{11}ClN_4O_2$. Calculated, %: C 57.32; H 3.50; N 17.83.

4-[2-(4-Chlorophenyl)hydrazinylidene]-1-phenylpyrazolidine-3,5-dione (7e). Orange granular solid from ethanol, yield 40.7%; mp 263-265°C. IR spectrum, ν, cm^{-1}: 3190 (NH), 3050 (aromatic CH), 2950 (aliphatic CH), 1710 (C=O), 1640 (C=O), 1580 (N=N). Mass spectrum, *m/z* (I_{rel}, %): 316 (7), 315 (12), 314

(19), 313 (48), 279 (5), 175 (1), 133 (12), 128 (18), 28 (100). Found, %: C 57.38; H 3.48; N 17.78. $C_{12}H_{16}ClN_4O_2$. Calculated, %: C 57.32; H 3.50; N 17.83.

4-[2-(3-Bromophenyl)hydrazinylidene]-1-phenylpyrazolidine-3,5-dione (7f). Orange flakes from ethanol, yield 46.9%; mp 262°C. IR spectrum, ν, cm^{-1}: 3150 (NH), 3050 (aromatic CH), 2850 (aliphatic CH), 1690 (C=O), 1660 (C=O), 1580 (N=N). Mass spectrum, *m/z* (I_{rel}, %): 360 (15), 359 (90), 358 (19), 357 (100), 172 (5), 170 (7), 134 (5). Found, %: C 50.22; H 3.11; N 15.61. $C_{15}H_{11}BrN_4O_2$. Calculated, %: C 50.2; H 3.12; N 15.63.

Benzaldhyde 3-bromophenylhydrazone (8d). Pale-yellow granular solid from ethanol, yield 40.8%; mp 125°C. IR spectrum, ν, cm^{-1}: 3300 (NH), 3050 (aromatic CH), 1590 (C=N). Found, %: C 57.71; H 4.10; N 10.02. $C_{13}H_{11}BrN_2$. Calculated, %: C 56.69; H 3.99; N 10.18.

4-[2-(2-Nitrophenyl)hydrazinylidene]-1-phenylpyrazolidine-3,5-dione (7g). Brown granular solid from ethanol, yield 51.7%; mp 280°C. IR spectrum, ν, cm^{-1}: 3290 (NH), 3050 (aromatic CH), 2900 and 2850 (aliphatic CH), 1690 (C=O), 1660 (C=O), 1580 (N=N), 1530 (C=N), 1490 (C–NO_2). Mass spectrum, *m/z*, (I_{rel}, %): 325 [M^+] (25), 324 (100), 137 (27), 135 (11). Found, %: C 55.41; H 3.32; N 21.42. $C_{15}H_{11}N_5O_4$. Calculated, %: C 55.34; H 3.38; N 21.52.

Benzaldehyde 2-Nitrophenylhydrazone (8b). Dark-red flakes from ethanol, yield 41.9%; mp 130-133°C. IR spectrum, ν, cm^{-1}: 3295 (NH), 3050 (aromatic CH), 1610 (C=N), 1500 (C–NO_2). Found, %: C 64.73; H 4.62; N 17.51. $C_{13}H_{11}N_3O_2$. Calculated, %: C 64.67; H 4.56; N 17.41.

4-[2-(3-Nitrophenyl)hydrazinylidene]-1-phenylpyrazolidine-3,5-dione (7h). Orange flakes from ethanol, yield 43.1%; mp 158-187°C. IR spectrum, ν, cm^{-1}: 3200 (NH), 3030 (aromatic CH), 2900 (aliphatic CH), 1710 (C=O), 1680 (C=O), 1610 (C=N), 1580 (N=N). Mass spectrum, *m/z* (I_{rel}, %): 325 [M^+] (16), 324 (56), 137 (45), 134 (6), 133 (38), 106 (20), 77 (100).

Benzaldehyde 3-Nitrophenylhydrazone (8c). Orange flakes from ethanol, yield 39.5%; mp 198°C. IR spectrum, ν, cm^{-1}: 3300 (NH), 3050 (aromatic CH), 1610 (C=N), 1540 (C–NO_2).

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