Multicomponent condensation of 1,2-dihydropyrazol-3-one derivatives with carbonyl compounds and Meldrum´s acid*

B. V. Lichitskii, A. O. Osipov, A. N. Komogortsev, A. A. Dudinov, and M. M. Krayushkin*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 119991 Moscow, Russian Federation. E-mail: mkray@ioc.ac.ru

A convenient method for the synthesis of earlier unknown 3-aryl-3-(3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)propionic acid derivatives was developed based on the multicomponent condensation of 1,2-dihydropyrazol-3-ones, carbonyl compounds, and Meldrum´s acid.

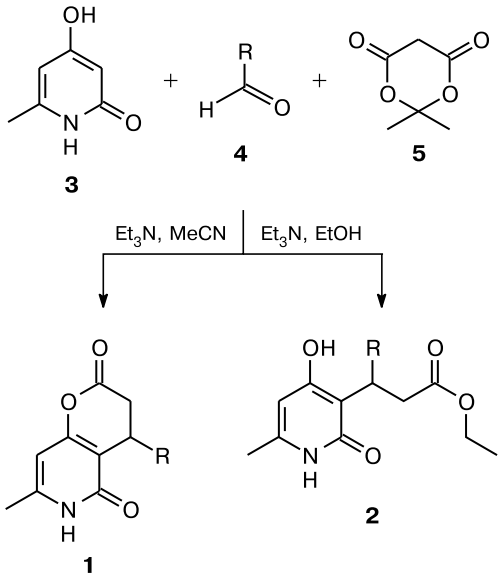
Key words: multicomponent condensation, Meldrum´s acid, 1,2-dihydropyrazol-3-ones, 3-arylpropionic acids.

1,2-Dihydropyrazol-3-one derivatives possess a wide range of biological activity. For example, the products containing a 1,2-dihydropyrazol-3-one fragment are suggested as neuroprotectors and antiemetics.[1,2] Therefore, the development of new methods for the synthesis of these products is an important direction of synthetic chemistry. The use of multicomponent reactions as an efficient instrument in the development and modification of various types of heterocyclic systems,[3,4] in our opinion, is a convenient approach to the preparation of a wide number of products with certain substituents.

Earlier, we have suggested the methods for the synthesis of fused dihydropyranones **1** and substituted 3-arylpropionic acid esters **2** based on the multicomponent condensation of hydroxypyridone **3** with aldehydes **4** and Meldrum´s acid (**5**).[5] Note that the direction of the reaction depends on the type of the solvent used: the process in acetonitrile led to the formation of dihydropyranones **1**, whereas esters **2** were formed in alcohols (Scheme 1).

The purpose of the present work is the studies of the multicomponent reaction of 1,2-dihydropyrazol-3-one derivatives **6** with carbonyl compounds and Meldrum´s acid (**5**), as well as establishing structure and studies of properties of the products formed. We have shown that the reaction of pyrazolones **6** with aldehydes **4** and Meldrum´s acid (**5**) in methanol in the presence of triethylamine used as a base led to methyl 3-aryl-3-(3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)propionates **7** in good yields (Scheme 2). Most likely, unstable dihydropyranones **8** are initially formed as a result of the multicomponent reaction, which when treated with methanol undergo the pyran ring opening, leading to the target esters **7**.

Scheme 1



Similarly to the multicomponent condensation for hydroxypyridone **3** considered above,[5] we studied the reaction of pyrazolones **6** with aldehydes **4** and Meldrum´s acid (**5**) in acetonitrile in order to synthesize dihydropyranones **8**. However, this the reaction did not lead to the expected results because of the low stability of compound **8** under conditions of the process. We suggested that the addition of an extra nucleophilic reagent to the reaction mixture would lead to the formation of the corresponding pyran ring opening product. In fact, the use of ammonium acetate, serving as a source of ammonia, led to 3-aryl-3-(3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)propionic acid amides **9** in good yields (Scheme 2).

* On the occasion of the 100th anniversary of the birth of Academician N. K. Kochetkov (1915—2005).

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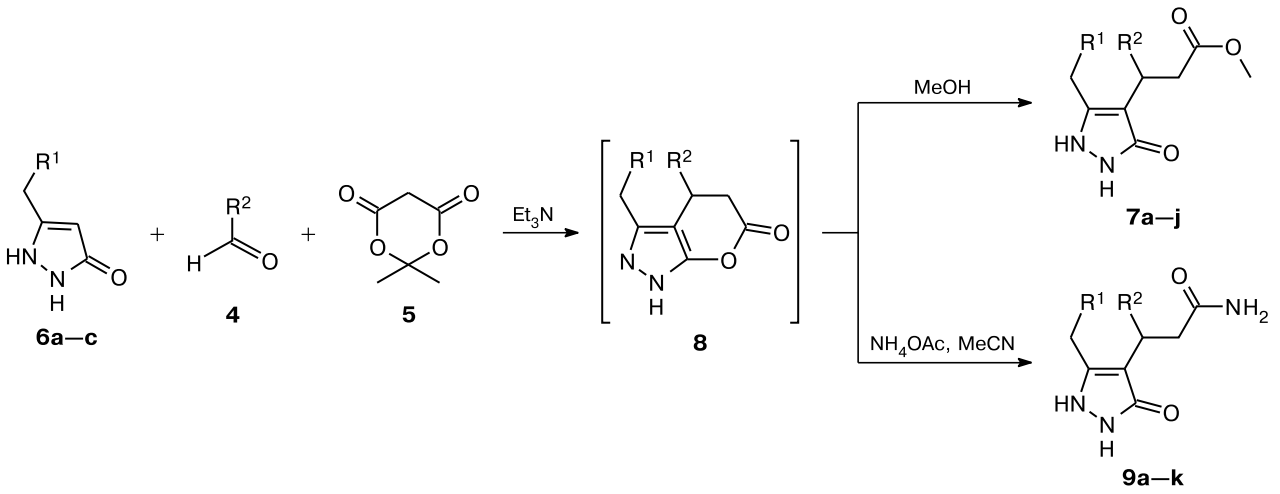
Scheme 2



6	R^1
a	H
b	Ph
c	EtO_2C

7	R^1	R^2
a	H	2-Cl-C_6H_4
b	H	2-MeO-C_6H_4
c	H	4-MeO-C_6H_4
d	H	2,5-$(MeO)_2$-C_6H_3
e	H	Ph

7	R^1	R^2
f	Ph	2-NO_2-C_6H_4
g	Ph	4-MeO-C_6H_4
h	Ph	Ph
i	Ph	4-Cl-C_6H_4
j	Ph	2,4-Cl_2-C_6H_3

9	R^1	R^2
a	H	3-Py
b	H	4-MeO-C_6H_4
c	H	4-Py
d	H	2,4-Cl_2-C_6H_3
e	H	3,4,5-$(MeO)_3$-C_6H_2

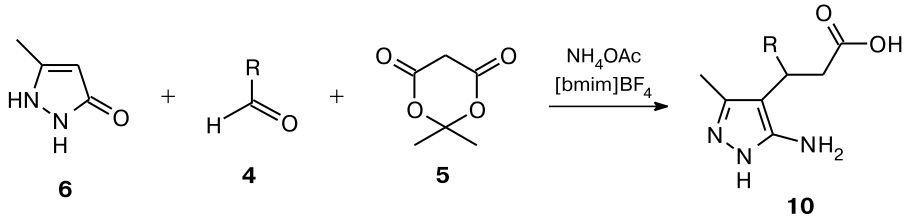
9	R^1	R^2
f	H	Ph
g	H	4-HO-3-MeO-C_6H_3
h	EtO_2C	3,4-$(MeO)_2$-C_6H_3
i	EtO_2C	4-MeO-C_6H_4
j	EtO_2C	4-Cl-C_6H_4
k	Ph	4-MeO-C_6H_4

Such multicomponent reactions of 1,2-dihydropyrazol-3-ones **6**, aldehydes **4**, and Meldrum´s acid (**5**) have been studied earlier.[6] When the reaction was carried out in an ionic liquid using ammonium acetate, the authors obtained products **10** (Scheme 3). A comparison of the ^1H and ^{13}C NMR spectroscopy data, as well as melting points, showed that products **10** obtained in the work[6] are identical to compounds **9** synthesized by us in this work. We used 2D $^1H—^{13}C$ HMBC NMR spectroscopy to unambiguously confirm the structure **9**.

Figure 1 shows a fragment of the 2D $^1H—^{13}C$ HMBC spectrum of compound **9d**. The spectrum exhibits the cross-peaks between the signals for the amide protons H(9), H(9´) (δ 6.75 and 7.32) and carbon atom C(8) (δ 172.33), as well as a correlation of the signal for the protons of the methylene fragment H(7) (δ 2.78) with the signal for carbon atom C(8) (δ 172.33). These data indicate the presence of the CH_2CONH_2 fragment in the structure of product **9d** and, hence, unambiguously confirm the structure of the products suggested by us in this work.

In the reactions considered above, various aldehydes were used as the carbonyl component. It is obvious that the involvement of ketones into the process under study will make it possible to considerably broaden the possibilities of this method and vary the range of synthesized products. As in the case of hydroxypyridone **3** (see Ref. 5), the multicomponent condensation of pyrazol-3-one **6b**, acetone, and Meldrum´s acid (**5**) in methanol in the presence of triethylamine did not lead to the expected products. Therefore, to accomplish the synthesis of the target products we preliminary obtained 5-isopropylidene-2,2-dimethyl-[1,3]dioxane-4,6-dione **11**, the product of the condensation of acetone and Meldrum´s acid. Its reaction with pyrazol-3-one **6b** in methanol and triethylamine as a base led to the synthesis of ester **12** in good yield (Scheme 4). Note that for the increase in the yield of the target product **12**, we used a two-fold excess of isopropyl-

Scheme 3



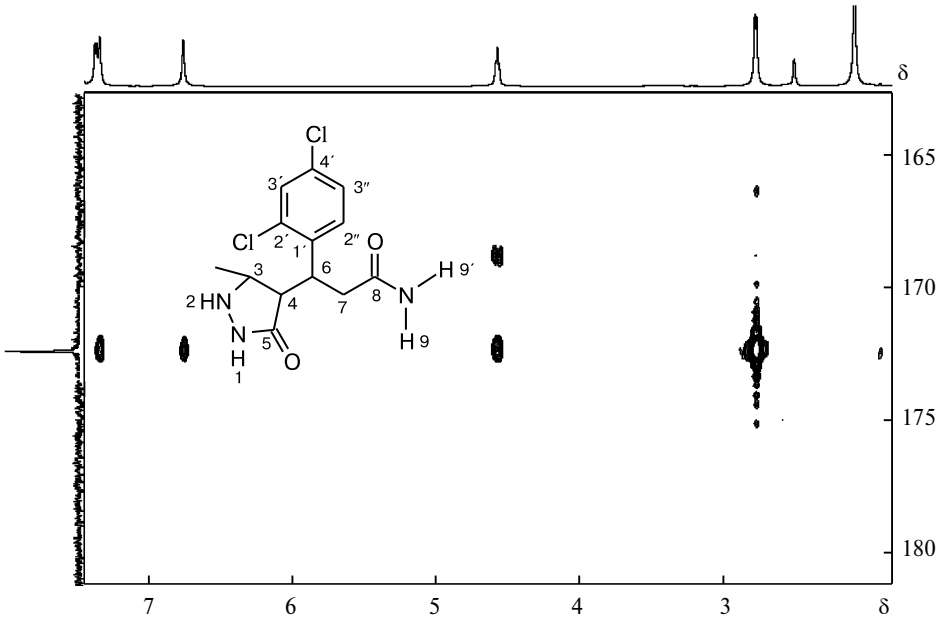
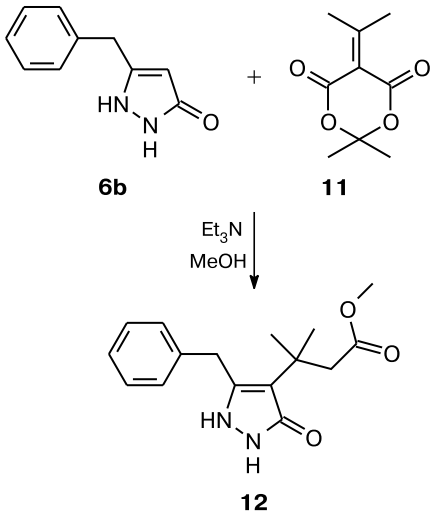


Fig. 1. A fragment of the 2D $^{1}H—^{13}C$ HMBC spectrum of compound **9d** (600 MHz, DMSO-d_6).

idene derivative **11**, which decomposes to a considerable degree in the process of the reaction. In contrast to the reaction involving hydroxypyridone **3**, for which the cyclic dihydropyranone was exclusively obtained,[5] only ester **12** was synthesized when pyrazole **6b** was used.

Scheme 4



In conclusion, we studied a multicomponent condensation of 1,2-dihydropyrazol-3-ones with carbonyl compounds and Meldrum´s acid and showed that the use of methanol as the solvent leads to the formation of methyl 3-aryl-3-(3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)propionates **7**. Carrying out the reaction in acetonitrile in the presence of ammonium acetate allowed us to synthesize 3-aryl-3-(3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)propionic amides **9**. Apparently the processes under study proceed through the step of the formation of dihydropyranones **8**, which were not isolated in the free form in the case of 1,2-dihydropyrazol-3-one derivatives because of their low stability.

Experimental

^{1}H, ^{13}C, and ^{1}H-^{13}C HMBC NMR spectra were recorded on Bruker AM-300 and Bruker AM-600 spectrometers (300 and 600 MHz) in DMSO-d_6. Electrospray ionization (ESI) high resolution mass spectra were recorded on a Bruker micrOTOF II instrument. Melting points were measured on a Boetius heating stage and were not corrected.

Compound **6a** is commercially available, compounds **6c**[7] and **11**[8] were obtained according to the procedures described in the literature.

5-Benzyl-1,2-dihydropyrazol-3-one (6b). 4-Dimethylaminopyridine (4.88 g, 0.04 mol) and Meldrum´s acid (**5**) (5.76 g, 0.04 mol) were dissolved in dichloromethane (40 mL). Phenylacetic acid (5.44 g, 0.04 mol) was added to this solution with stirring, then, a solution of DCC (10.30 g, 0.05 mol) in dichloromethane (20 mL) was added dropwise. The mixture obtained was stirred for 6 h and concentrated to a dry residue. Water (100 mL) was added to this residue, stirred for 30 min, a precipitate of *N*,*N*´-dicyclohexylurea was filtered off. The filtrate was concentrated to a dry residue. A solution of hydrazine hydrate (6.00 g, 0.12 mol) in ethanol (10 mL) was added to this residue, and the mixture was refluxed for 2 h. Then, acetic acid (12.00 g, 0.2 mol) was added and concentrated. Water (40 mL) was added to the residue, and the product was filtered. The yield was 86%, m.p. 183—185 °C (*cf.* Ref. 9: m.p. 184 °C). ^{1}H NMR (DMSO-d_6), δ: 3.79 (s, 2 H, CH_2); 5.22 (s, 1 H, CH); 7.50 (m, 5 H, H_{Ar}); 10.51 (br.s, 2 H, NH). ^{13}C NMR (DMSO-d_6), δ: 32.01, 88.60, 126.10, 128.30, 139.19, 143.23, 160.67. MS (ESI), *m/z:* found:

175.0866 $[M + H]^+$. $C_{10}H_{10}N_2O$. Calculated: [M + H] = = 175.0871.

Methyl 3-(5-alkyl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)-3-arylpropionates 7a-j (general procedure). A corresponding pyrazole **6** (2 mol), Meldrum´s acid (**5**) (0.33 g, 2.3 mmol), a corresponding aldehyde **4** (2.1 mmol), and triethylamine (0.23 g, 2.3 mmol) were mixed in methanol (5 mL). The reaction mixture was refluxed 2 h and concentrated dry, the residue was recrystallized from aqueous methanol. A precipitate formed was filtered and washed with aqueous methanol on the filter.

3-(2-Chlorophenyl)-3-(5-methyl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)propionic acid methyl ester (7a). The yield was 69%, m.p. 207—209 °C. ^{1}H NMR (DMSO-d_6), δ: 2.06 (s, 3 H, CH_3); 2.92 (dd, 1 H, H—C—H, *J* = 15.7 Hz, *J* = 9.3 Hz); 3.12 (dd, 1 H, H—C—H, *J* = 15.7 Hz, *J* = 6.5 Hz); 3.51 (s, 3 H, OCH_3); 4.60 (t, 1 H, CH, *J* = 6.9 Hz); 7.16—7.61 (m, 4 H, H_{Ar}); 10.43 (br.s, 2 H, NH). ^{13}C NMR (DMSO-d_6), δ: 10.09, 32.55, 37.62, 51.17, 100.75, 126.99, 127.63, 129.05, 129.23, 132.05, 136.78, 141.05, 159.52, 171.60. Found (%): C, 57.24; H, 5.20; N, 9.36. $C_{14}H_{15}ClN_2O_3$ (294.74). Calculated (%): C, 57.05; H, 5.13; N, 9.50.

3-(2-Methoxyphenyl)-3-(5-methyl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)propionic acid methyl ester (7b). The yield was 54%, m.p. 199—201 °C. ^{1}H NMR (DMSO-d_6), δ: 2.06 (s, 3 H, CH_3); 2.84 (dd, 1 H, H—C—H, *J* = 15.2 Hz, *J* = 9.7 Hz); 3.08 (dd, 1 H, H—C—H, *J* = 15.2 Hz, *J* = 5.5 Hz); 3.49 (s, 3 H, OCH_3); 3.76 (s, 3 H, OCH_3); 4.51 (t, 1 H, CH, *J* = 6.5 Hz); 6.82—7.31 (m, 4 H, H_{Ar}); 10.30 (br.s, 2 H, NH). ^{13}C NMR (DMSO-d_6), δ: 9.89, 28.63, 37.29, 51.01, 55.27, 101.54, 110.47, 119.97, 126.91, 127.66, 131.83, 136.68, 155.90, 159.70, 172.12. Found (%): C, 61.85; H, 6.30; N, 9.46. $C_{15}H_{18}N_2O_4$ (290.32). Calculated (%): C, 62.06; H, 6.25; N, 9.65.

3-(4-Methoxyphenyl)-3-(5-methyl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)propionic acid methyl ester (7c). The yield was 57%, m.p. 197—199 °C. ^{1}H NMR (DMSO-d_6), δ: 2.02 (s, 3 H, CH_3); 3.01 (dd, 1 H, H—C—H, *J* = 15.5 Hz, *J* = 9.5 Hz); 3.18 (dd, 1 H, H—C—H, *J* = 15.5 Hz, *J* = 6.5 Hz); 3.49 (s, 3 H, OCH_3); 3.69 (s, 3 H, OCH_3); 4.11 (t, 1 H, CH, *J* = 6.5 Hz); 7.21 (d, 2 H, H_{Ar}, *J* = 7.8 Hz); 7.71 (d, 2 H, H_{Ar}, *J* = 7.8 Hz); 10.36 (br.s, 2 H, NH). ^{13}C NMR (DMSO-d_6), δ: 9.97, 35.51, 51.03, 54.87, 102.78, 113.46, 113.62, 128.09, 136.27, 136.53, 157.37, 159.25, 172.03. Found (%): C, 62.35; H, 6.37; N, 9.48. $C_{15}H_{18}N_2O_4$ (290.32). Calculated (%): C, 62.06; H, 6.25; N, 9.65.

3-(2,5-Dimethoxyphenyl)-3-(5-methyl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)propionic acid methyl ester (7d). The yield was 60%, m.p. 182—184 °C. ^{1}H NMR (DMSO-d_6), δ: 2.06 (s, 3 H, CH_3); 2.84 (dd, 1 H, H—C—H, *J* = 15.4 Hz, *J* = 9.6 Hz); 3.06 (dd, 1 H, H—C—H, *J* = 15.4 Hz, *J* = 6.5 Hz); 3.50 (s, 3 H, OCH_3); 3.65 (s, 3 H, OCH_3); 3.73 (s, 3 H, OCH_3); 4.53 (t, 1 H, CH, *J* = 6.5 Hz); 6.67—6.94 (m, 3 H, H_{Ar}); 10.54 (br.s, 2 H, NH). ^{13}C NMR (DMSO-d_6), δ: 9.83, 28.74, 37.35, 51.01, 55.07, 55.82, 101.49, 110.44, 111.35, 114.79, 133.20, 136.72, 150.10, 152.87, 159.61, 172.03. Found (%): C, 60.23; H, 6.39; N, 8.89. $C_{16}H_{20}N_2O_5$ (320.35). Calculated (%): C, 59.99; H, 6.29; N, 8.74.

3-(5-Methyl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)-3-phenylpropionic acid methyl ester (7e). The yield was 61%, m.p. 188—190 °C. ^{1}H NMR (DMSO-d_6), δ: 2.03 (s, 3 H, CH_3); 3.03 (dd, 1 H, H—C—H, *J* = 15.3 Hz, *J* = 9.5 Hz); 3.11 (dd, 1 H, H—C—H, *J* = 15.3 Hz, *J* = 7.2 Hz); 3.49 (s, 3 H, OCH_3); 4.16 (t, 1 H, CH, *J* = 7.7 Hz); 7.13—7.32 (m, 5 H, H_{Ar}); 10.35 (br.s, 2 H, NH). ^{13}C NMR (DMSO-d_6), δ: 10.18, 36.26, 38.34, 51.08, 102.47, 126.47, 128.06, 128.29, 136.40, 144.50, 159.28, 172.00. Found (%): C, 64.42; H, 6.15; N, 10.90. $C_{14}H_{16}N_2O_3$ (260.30). Calculated (%): C, 64.60; H, 6.20; N, 10.76.

3-(5-Benzyl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)-3-(2-nitrophenyl)propionic acid methyl ester (7f). The yield was 75%, m.p. 211—213 °C. ^{1}H NMR (DMSO-d_6), δ: 2.96 (dd, 1 H, H—C—H, *J* = 15.8 Hz, *J* = 7.1 Hz); 3.09 (dd, 1 H, H—C—H, *J* = 15.8 Hz, *J* = 7.8 Hz); 3.45 (s, 3 H, OCH_3); 3.77 (m, 2 H, CH_2); 4.81 (t, 1 H, CH, *J* = 7.2 Hz); 6.76—7.80 (m, 9 H, H_{Ar}); 10.79 (br.s, 2 H, NH). ^{13}C NMR (DMSO-d_6), δ: 30.08, 30.79, 38.49, 51.25, 100.90, 123.72, 126.01, 127.36, 127.83, 128.17, 129.93, 132.81, 138.11, 138.25, 139.62, 148.57, 159.46, 171.25. Found (%): C, 63.20; H, 4.91; N, 11.17. $C_{20}H_{19}N_3O_5$ (381.39). Calculated (%): C, 62.99; H, 5.02; N, 11.02.

3-(5-Benzyl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)-3-(4-methoxyphenyl)propionic acid methyl ester (7g). The yield was 52%, m.p. 193—195 °C. ^{1}H NMR (DMSO-d_6), δ: 2.92 (dd, 1 H, H—C—H, *J* = 15.6 Hz, *J* = 7.2 Hz); 3.09 (dd, 1 H, H—C—H, *J* = 15.6 Hz, *J* = 7.9 Hz); 3.45 (s, 3 H, OCH_3); 3.68 (s, 3 H, OCH_3); 3.79 (m, 2 H, CH_2); 4.14 (t, 1 H, CH, *J* = 7.3 Hz); 6.71—7.10 (m, 9 H, H_{Ar}); 11.30 (br.s, 2 H, NH). ^{13}C NMR (DMSO-d_6), δ: 30.26, 35.35, 38.82, 51.02, 54.87, 102.93, 113.29, 126.03, 128.16, 128.19, 128.21, 136.39, 138.80, 138.85, 157.30, 159.14, 171.94. Found (%): C, 69.04; H, 6.17; N, 7.82. $C_{21}H_{22}N_2O_4$ (366.42). Calculated (%): C, 68.84; H, 6.05; N, 7.65.

3-(5-Benzyl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)-3-phenylpropionic acid methyl ester (7h). The yield was 51%, m.p. 175—177 °C. ^{1}H NMR (DMSO-d_6), δ: 2.95 (dd, 1 H, H—C—H, *J* = 15.7 Hz, *J* = 7.2 Hz); 3.05 (dd, 1 H, H—C—H, *J* = 15.7 Hz, *J* = 7.8 Hz); 3.46 (s, 3 H, OCH_3); 3.80 (m, 2 H, CH_2); 4.19 (t, 1 H, CH, *J* = 7.2 Hz); 7.05—7.26 (m, 10 H, H_{Ar}); 11.54 (br.s, 2 H, NH). ^{13}C NMR (DMSO-d_6), δ: 30.28, 36.16, 38.52, 51.05, 102.61, 125.76, 126.05, 127.21, 127.92, 128.21, 138.75, 139.07, 144.34, 159.22, 171.90. Found (%): C, 71.22; H, 6.08; N, 8.45. $C_{20}H_{20}N_2O_3$ (336.39). Calculated (%): C, 71.41; H, 5.99; N, 8.33.

3-(5-Benzyl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)-3-(4-chlorophenyl)propionic acid methyl ester (7i). The yield was 53%, m.p. 163—165 °C. ^{1}H NMR (DMSO-d_6), δ: 2.98 (dd, 1 H, H—C—H, *J* = 15.5 Hz, *J* = 7.2 Hz); 3.00 (dd, 1 H, H—C—H, *J* = 15.5 Hz, *J* = 7.9 Hz); 3.46 (s, 3 H, OCH_3); 3.82 (m, 2 H, CH_2); 4.18 (t, 1 H, CH, *J* = 7.9 Hz); 7.05—7.25 (m, 9 H, H_{Ar}); 10.55 (br.s, 2 H, NH). ^{13}C NMR (DMSO-d_6), δ: 30.27, 35.54, 38.35, 51.04, 102.11, 126.06, 127.78, 128.10, 128.40, 129.07, 130.33, 138.71, 139.14, 143,28, 159.12, 171.73. MS (ESI), *m/z*: found: 371.1157 $[M + H]^+$. $C_{20}H_{19}ClN_2O_3$. Calculated: [M + H] = 371.1162.

3-(5-Benzyl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)-3-(2,4-dichlorophenyl)propionic acid methyl ester (7j). The yield was 61%, m.p. 213—215 °C. ^{1}H NMR (DMSO-d_6), δ: 2.90 (dd, 1 H, H—C—H, *J* = 15.8 Hz, *J* = 8.5 Hz); 3.00 (dd, 1 H, H—C—H, *J* = 15.8 Hz, *J* = 8.5 Hz); 3.46 (s, 3 H, OCH_3); 3.81 (m, 2 H, CH_2); 4.61 (t, 1 H, CH, *J* = 7.9 Hz); 7.02—7.53 (m, 8 H, H_{Ar}); 10.50 (br.s, 2 H, NH). ^{13}C NMR (DMSO-d_6), δ: 30.36, 32.48, 37.57, 51.20, 100.46, 125.98, 127.16, 127.93, 128.11, 128.30, 130.48, 131.25, 132.85, 138.31, 139.44, 140.26, 159.49, 171.28. MS (ESI), *m/z*: found: 405.0767 $[M + H]^+$. $C_{20}H_{18}Cl_2N_2O_3$. Calculated: [M + H] = 405.0773.

3-Aryl-3-(5-alkyl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)propionic acid amides 9a—k (general procedure). A corresponding pyrazole **6** (2 mmol), Meldrum´s acid (**5**) (0.33 g, 2.3 mmol), a corresponding aldehyde **4** (2.1 mmol), ammonium acetate

(0.46 g, 6 mmol), and triethylamine (0.23 g, 2.3 mmol) were mixed in acetonitrile (5 mL). The reaction mixture was refluxed for 1 h and cooled. A precipitate formed was filtered and washed aqueous ethanol on the filter.

3-(5-Methyl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)-3-(pyridin-3-yl)-propionic acid amide (9a). The yield was 71%, m.p. 201—203 °C. ^{1}H NMR (DMSO-d_6), δ: 2.07 (s, 3 H, CH_3); 2.69 (dd, 1 H, H—C—H, *J* = 14.8 Hz, *J* = 8.0 Hz); 2.93 (dd, 1 H, H—C—H, *J* = 14.8 Hz, *J* = 6.0 Hz); 4.24 (t, 1 H, CH, *J* = 7.9 Hz); 6.67 (s, 1 H, H—N—H); 7.23—8.50 (m, 5 H, H_{Ar} + H—N—H); 10.44 (br.s, 2 H, NH). ^{13}C NMR (DMSO-d_6), δ: 10.06, 33.65, 39.22, 102.61, 123.14, 134.74, 136.74, 140.39, 146.80, 148.82, 159.33, 172.63. Found (%): C, 58.74; H, 5.66; N, 22.62. $C_{12}H_{14}N_4O_2$ (246.27). Calculated (%): C, 58.53; H, 5.73; N, 22.75.

3-(4-Methoxyphenyl)-3-(5-methyl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)propionic acid amide (9b). The yield was 56%, m.p. 217—219 °C. ^{1}H NMR (DMSO-d_6), δ: 2.02 (s, 3 H, CH_3); 2.63 (dd, 1 H, H—C—H, *J* = 14.4 Hz, *J* = 7.3 Hz); 2.81 (dd, 1 H, H—C—H, *J* = 14.4 Hz, *J* = 8.3 Hz); 3.69 (s, 3 H, OCH_3); 4.15 (t, 1 H, CH, *J* = 7.9 Hz); 6.63 (s, 1 H, H—N—H); 6.74 (d, 2 H, H_{Ar}, *J* = 8.2 Hz); 7.20 (d, 2 H, H_{Ar}, *J* = 8.2 Hz); 7.25 (s, 1 H, H—N—H); 10.36 (br.s, 2 H, NH). ^{13}C NMR (DMSO-d_6), δ: 10.16, 35.10, 40.19, 54.87, 103.71, 113.27, 128.23, 136.18, 137.31, 157.14, 159.30, 173.07. MS (ESI), *m/z*: found: 276.1343 $[M + H]^+$. $C_{14}H_{17}N_3O_3$. Calculated: [M + H] = 276.1348.

3-(5-Methyl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)-4-(pyridin-3-yl)-propionic acid amide (9c). The yield was 60%, m.p. 257—259 °C. ^{1}H NMR (DMSO-d_6), δ: 2.07 (s, 3 H, CH_3); 2.74 (dd, 1 H, H—C—H, *J* = 14.8 Hz, *J* =7.0 Hz); 2.92 (dd, 1 H, H—C—H, *J* = 14.8 Hz, *J* = 8.6 Hz); 4.25 (t, 1 H, CH, *J* = 7.5 Hz); 6.73 (s, 1 H, H—N—H); 7.23 (s, 1 H, H—N—H); 7.30 (d, 2 H, H_{Ar}, *J* = 5.2 Hz); 8.40 (d, 2 H, H_{Ar}, *J* = 5.2 Hz); 10.55 (br.s, 2 H, NH). ^{13}C NMR (DMSO-d_6), δ: 10.09, 35.26, 38.79, 101.97, 122.81, 136.61, 149.16, 153.71, 159.33, 172.53. Found (%): C, 58.74; H, 5.62; N, 22.90. $C_{12}H_{14}N_4O_2$ (246.27). Calculated (%): C, 58.53; H, 5.73; N, 22.75.

3-(2,4-Dichlorophenyl)-3-(5-methyl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)propionic acid amide (9d). The yield was 55%, m.p. 232—235 °C. ^{1}H NMR (DMSO-d_6), δ: 2.07 (s, 3 H, CH_3); 2.78 (d, 2 H, CH_2, *J* = 7.7 Hz); 4.40 (t, 1 H, CH, *J* = 7.7 Hz); 6.75 (s, 1 H, H—N—H); 7.32 (s, 1 H, H—N—H); 7.33—7.65 (m, 3 H, H_{Ar}); 10.53 (br.s, 2 H, NH). ^{13}C NMR (DMSO-d_6), δ: 10.35, 32.26, 38.94, 101.19, 126.89, 128.38, 130.80, 130.94, 133.37, 136.86, 140.84, 159.70, 172.33. Found (%): C, 49.88; H, 4.08; N, 13.51. $C_{13}H_{13}Cl_2N_3O_2$ (314.17). Calculated (%): C, 49.70; H, 4.17; N, 13.37.

3-(5-Methyl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)-3-(3,4,5-trimethoxyphenyl)propionic acid amide (9e). The yield was 89%, m.p. 246—248 °C. ^{1}H NMR (DMSO-d_6), δ: 2.06 (s, 3 H, CH_3); 2.69 (dd, 1 H, H—C—H, *J* = 14.5 Hz, *J* = 7.6 Hz); 2.83 (dd, 2 H, H—C—H, *J* = 14.5 Hz, *J* = 6.5 Hz); 3.60 (s, 3 H, OCH_3); 3.72 (s, 6 H, OCH_3); 4.13 (t, 1 H, CH, *J* = 7.7 Hz); 6.65 (s, 1 H, H—N—H); 7.18 (s, 1 H, H—N—H); 7.25 (s, 2 H, H_{Ar}); 10.48 (br.s, 2 H, NH). ^{13}C NMR (DMSO-d_6), δ: 10.19, 36.34, 40.05, 55.64, 59.83, 103.39, 104.70, 135.44, 136.33, 141.06, 152.34, 159.28, 172.99. MS (ESI), *m/z*: found: 336.1554 $[M + H]^+$. $C_{16}H_{21}N_3O_5$. Calculated: [M + H] = 336.1559.

3-(5-Methyl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)-3-phenylpropionic acid amide (9f). The yield was 74%, m.p. 236—238 °C. ^{1}H NMR (DMSO-d_6), δ: 2.03 (s, 3 H, CH_3); 2.71 (dd, 1 H, H—C—H, *J* = 14.6 Hz, *J* = 7.3 Hz); 2.86 (dd, 1 H, H—C—H, *J* = 14.6 Hz, *J* = 8.2 Hz); 4.21 (t, 1 H, CH, *J* = 7.60 Hz); 6.66 (s, 1 H, H—N—H); 7.06—7.31 (m, 6 H, H_{Ar} + H—N—H); 10.38 (br.s, 2 H, NH). ^{13}C NMR (DMSO-d_6), δ: 10.18, 35.91, 39.86, 103.41, 125.48, 127.31, 127.89, 136.34, 145.26, 159.37, 173.00. Found (%): C, 63.85; H, 6.25; N, 17.00. $C_{13}H_{15}N_3O_2$ (245.28). Calculated (%): C, 63.66; H, 6.16; N, 17.13.

3-(4-Hydroxy-3-methoxyphenyl)-3-(5-methyl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)propionic acid amide (9g). The yield was 63%, m.p. 235—237 °C. ^{1}H NMR (DMSO-d_6), δ: 2.07 (s, 3 H, CH_3); 2.56 (dd, 1 H, H—C—H, *J* = 14.5 Hz, *J* = 7.3 Hz); 2.66 (dd, 1 H, H—C—H, *J* = 14.5 Hz, *J* = 7.7 Hz); 3.68 (s, 3 H, O CH_3); 4.06 (t, 1 H, CH, *J* = 7.7 Hz); 6.76 (s, 1 H, H—N—H); 6.81—7.38 (m, 4 H, H_{Ar} + H—N—H); 8.61 (br.s, 1 H, OH); 10.53 (br.s, 2 H, NH). ^{13}C NMR (DMSO-d_6), δ: 10.21, 35.55, 40.38, 55.46, 103.84, 111.81, 114.87, 119.47, 136.29, 136.32, 144.33, 147.01, 159.33, 173.27. MS (ESI), *m/z*: found: 292.1292 $[M + H]^+$. $C_{14}H_{17}N_3O_4$. Calculated: [M + H] = 292.1297.

{4-[2-Carbamoyl-1-(3,4-dimethoxyphenyl)ethyl]-5-oxo-2,5-dihydro-1*H*-pyrazol-3-yl}acetic acid ethyl ester (9h). The yield was 49%, m.p. 164—166 °C. ^{1}H NMR (DMSO-d_6), δ: 1.12 (t, 3 H, CH_3, *J* = 7.0 Hz); 2.66 (dd, 1 H, H—C—H, *J* = 15.2 Hz, *J* = 7.4 Hz); 2.80 (dd, 1 H, H—C—H, *J* = 15.2 Hz, *J* = 7.9 Hz); 3.51 (m, 2 H, CH_2); 3.71 (s, 6 H, 2 OCH_3); 3.98 (q, 2 H, CH_2, *J* = 6.6 Hz); 4.14 (t, 1 H, CH, *J* = 7.0 Hz); 6.65 (s, 1 H, H—N—H), 6.77—6.94 (m, 3 H, H_{Ar}); 7.25 (s, 1 H, H—N—H); 11.12 (br.s, 2 H, NH). ^{13}C NMR (DMSO-d_6), δ: 13.85, 30.73, 35.27, 39.52, 55.26, 55.47, 60.41, 104.71, 111.41, 111.92, 119.29, 133.31, 137.07, 146.80, 148, 15, 158.72, 169.34, 173.05. Found (%): C, 57.50; H, 6.05; N, 10.98. $C_{18}H_{23}N_3O_6$ (377.40). Calculated (%): C, 57.29; H, 6.14; N, 11.13.

{4-[2-Carbamoyl-1-(4-methoxyphenyl)ethyl]-5-oxo-2,5-dihydro-1*H*-pyrazol-3-yl}acetic acid ethyl ester (9i). The yield was 64%, m.p. 193—195 °C. ^{1}H NMR (DMSO-d_6), δ: 1.12 (t, 3 H, CH_3, *J* = 7.1 Hz); 2.65 (dd, 1 H, H—C—H, *J* = 14.8 Hz, *J* = 7.0 Hz); 2.80 (dd, 1 H, H—C—H, *J* = 14.8 Hz, *J* = 8.4 Hz); 3.49 (m, 2 H, CH_2); 3.68 (s, 3 H, OCH_3); 3.99 (q, 2 H, CH_2, *J* = 7.1 Hz); 4.15 (t, 1 H, CH, *J* = 7.0 Hz); 6.65 (s, 1 H, H—N—H); 6.76 (d, 2 H, H_{Ar}, *J* = 8.3 Hz); 7.19 (d, 2 H, H_{Ar}, *J* = 8.3 Hz); 7.24 (s, 1 H, H—N—H); 11.20 (br.s, 2H, NH). ^{13}C NMR (DMSO-d_6), δ: 13.85, 30.78, 34.81, 39.40, 54.86, 60.43, 104.69, 113.09, 128.40, 133.32, 136.49, 157.15, 158;75, 169.26, 173.03. MS (ESI), *m/z*: found: 348.1554 $[M + H]^+$. $C_{17}H_{21}N_3O_5$. Calculated: [M + H] = = 348.1559.

{4-[2-Carbamoyl-1-(4-chlorophenyl)ethyl]-5-oxo-2,5-dihydro-1*H*-pyrazol-3-yl}acetic acid ethyl ester (9j). The yield was 57%; m.p. 192—194 °C. ^{1}H NMR (DMSO-d_6), δ: 1.10 (t, 3 H, CH_3, *J* = 7.0 Hz); 2.65 (dd, 1 H, H—C—H, *J* = 14.8 Hz, *J* = 7.0 Hz); 2.86 (dd, 1 H, H—C—H, *J* = 14.8 Hz, *J* = 8.2 Hz); 3.52 (m, 2 H, CH_2); 3.97 (q, 2 H, CH_2, *J* = 7.0 Hz); 4.21 (t, 1 H, CH, *J* = 7.0 Hz); 6.69 (s, 1 H, H—N—H); 7.31 (m, 5 H, H_{Ar} + H—N—H); 11.12 (br.s, 2 H, NH). ^{13}C NMR (DMSO-d_6), δ: 13.82, 30.75, 35.10, 39.62, 60.47, 103.93, 127.59, 129.37, 130.08, 133.49, 143.49, 158.78, 169.20, 172;70. MS (ESI), *m/z*: found: 352.1059 $[M + H]^+$. $C_{16}H_{18}ClN_3O_4$. Calculated: [M + H] = 352.1064.

3-(5-Benzyl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)-3-(4-methoxyphenyl)propionic acid amide (9k). The yield was 53%, m.p. 203—204 °C. ^{1}H NMR (DMSO-d_6), δ: 2.64 (dd, 1 H, H—C—H, *J* = 14.7 Hz, *J* = 7.1 Hz); 2.83 (dd, 1 H, H—C—H, *J* = 14.7 Hz, *J* = 8.8 Hz); 3.67 (s, 3 H, OMe); 3.80 (m, 2 H, CH_2); 4.21 (t, 1 H, CH, *J* = 7.5 Hz); 6.65 (s, 1 H, H—N—H); 6.68—7.26 (m, 10 H,

H_{Ar} + H—N—H); 10.41 (br.s, 2 H, NH). ^{13}C NMR (DMSO-d_6), δ: 30.31, 35.13, 40.33, 54.85, 103.88, 113.07, 125.99, 128.19, 128.27, 128.39, 137.03, 138.93, 138.97, 157.09, 159.25, 173.04. Found (%): C, 68.55; H, 5.89; N, 12.09. $C_{20}H_{21}N_3O_3$ (351.41). Calculated (%): C, 68.36; H, 6.02; N, 11.96.

3-(5-Benzyl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)-3-methylbutanoic acid methyl ester 12. Pyrazole **6b** (0.35 g, 2 mmol), 5-isopropylidene-2,2-dimethyl-1,3-dioxane-4,6-dione **11** (0.74 g, 4 mmol), and triethylamine (0.23 g, 2.3 mmol) were mixed in methanol (5 mL). The reaction mixture was refluxed for 2 h and concentrated, the residue was recrystallized from aqueous methanol. A precipitate formed was filtered and washed with aqueous methanol on the filter. The yield was 43%, m.p. 188—190 °C. ^{1}H NMR (DMSO-d_6), δ: 1.24 (s, 6 H, 2 CH_3); 2.59 (s, 2 H, CH_2); 3.44 (s, 3 H, OCH_3); 3.96 (s, 2 H, CH_2); 7.06 (d, 2 H, H_{Ar}, J = 7.4 Hz); 7.18 (m, 1 H, H_{Ar}); 7.28 (m, 2 H, H_{Ar}); 11,01 (br.s, 2 H, NH). ^{13}C NMR (DMSO-d_6), δ: 27.79, 31.78, 32.68, 45.12, 50.60, 106.34, 125.91, 127.60, 128.24, 136.67, 139.87, 159.39, 171;60. Found (%): C, 66.44; H, 6.87; N, 9.61. $C_{16}H_{20}N_2O_3$ (288.35). Calculated (%): C, 66.65; H, 6.99; N, 9.72.

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