

Synthesis and structural characterization of products condensation 4-carboxy-1-(4-styrylcarbonylphenyl)-2-pyrrolidinones with hydrazines

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Abstract

The synthesis of some new chalcones is described. A series of the pyrazole and pyrazoline type derivatives were obtained by the condensation of the chalcones with hydrazine and phenylhydrazine. All compounds were characterized using NMR, IR, MS techniques. Computer molecular modeling assisted for NMR spectral analysis.

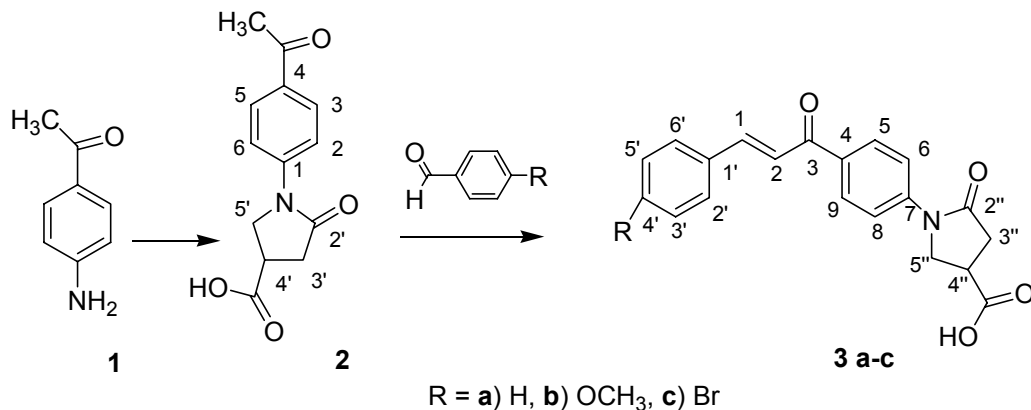
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Introduction

The chalcones are the convenient intermediates for the synthesis five,^[1,2] six^[1,3] and seven members^[4] heterocycles, often have exhibited diverse biological activity. Some pyrazoline derivatives were used as the bacteriostatic, fungicidal, and anticancer agents.^[5] We continued our interest in the chemistry of N-substituted amino acids and the products of their cyclization, in this case – 1,3-disubstituted 2-pyrrolidinones. The structure of newly synthesized compounds was mainly characterized by NMR spectroscopy. The influence of the 5-substituent on the carbons and protons of pyrazoline and pyrazole derivatives has been discussed. The substitution of benzene ring as the starting chalcones **3a-c**,^[6-8] as the pyrazoline^[2, 9-18] and pyrazole^[19-34] derivatives was taken into account. The average increments of pyrazoline and pyrazole for aromatic carbon atoms as for monosubstituted benzene rings were determined. The calculated extended Hückel charges followed the carbons chemical shifts verify the assignment.

Results and Discussion

The starting product - 1-(4-acetylphenyl)-4-carboxy-2-pyrrolidinone **2** was synthesized according to the known method by the refluxing 4-aminoacetophenone **1** with itaconic acid in water. The chalcones **3a-c** were obtained in good yields by base (NaOH) catalyzed aldol condensation of the substituted acetophenone derivative **2** and the substituted benzaldehydes in ethanol (Scheme 1).

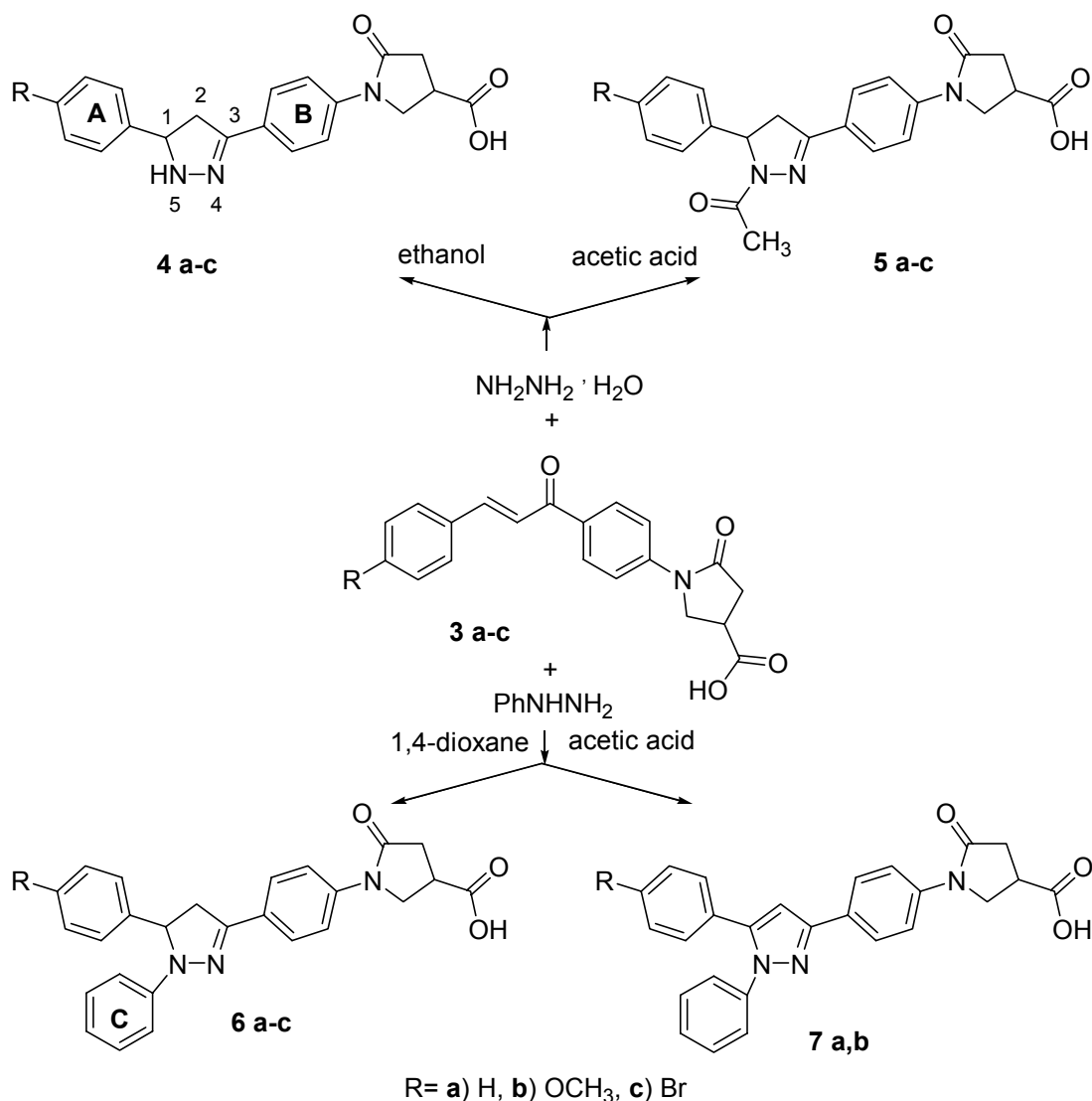


Scheme 1. Synthesis of 4-carboxy-1-(4-styrylcarbonylphenyl)-2-pyrrolidinones.

Compounds **3a-c** were tested as precursors in the synthesis of the pyrazole and the pyrazoline derivatives (Scheme 2) by reaction with hydrazine hydrate or phenylhydrazine.

The reactions between the chalcones **3a-c** and the hydrazine hydrate in refluxing ethanol and the acetic acid was monitored by TLC. After 5 hours all starting material was consumed. Condensation of the chalcones **3a-c** and the hydrazine hydrate in ethanol gave the corresponding 1-[4-(5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)phenyl]-5-oxo-pyrrolidine-3-carboxylic acids **4a-c**, while in acetic acid - 1-[4-(1-acetyl-5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)phenyl]-5-oxopyrrolidine-3-carboxylic acids **5a-c** were formed. The chalcones **3a-c** reacted with phenylhydrazine in boiling 1,4-dioxane resulting in the formation of 1-[4-(1,5-diaryl-4,5-dihydro-1*H*-pyrazol-3-yl)phenyl]-5-oxopyrrolidine-3-carboxylic acids **6a-c**, while in acetic acid - pyrazole derivatives **7 a,b**.

The structure of the above mentioned compounds was confirmed by NMR, IR and MS spectral data. The most comprehensive analytical data were obtained by NMR studies. The assignment was made on the substituents additivity rules, spectral characteristics of structurally related compounds, signal intensities and multiplicities. An APT ¹³C NMR experiment was used to prove the interpretation of the carbon resonances in some cases. The data on ¹H and ¹³C NMR chemical shifts are presented in experimental part. The carbon atoms are marked arbitrary according to the numbering given in Scheme 1 and Scheme 2.



Scheme 2. Synthesis of substituted pyrazoline and pyrazole derivatives.

The studied compounds possess nonsubstituted (**a**), OCH₃ (**b**) and Br (**c**) aromatic derivatives. Due to the substituent OCH₃ ¹³C NMR chemical shift of C-2 atom in compound **3b** is shielded 2.5 ppm, while the atoms C-1 and C-3 were much less shielded (0.2 ppm and 0.1 ppm). Due to the Br substitution observed the low shielding effect 1.0 ppm for the C-1, and deshielding 0.7 ppm. for the C-2 atom. ¹H NMR spectra showed a weak shielding for H-1 and H-2 protons, especially for the H-2 proton (0.17 ppm) due to the Br substitution.

Values of 63.7 ppm, 40.6 ppm and 148.3 ppm in ¹³C NMR spectra of compounds **4a-c** confirmed formation of the pyrazoline fragment after the condensation of the compounds **3a-c** with the hydrazine hydrate in ethanol. Substitution of the aromatic ring (OCH₃, Br) caused a low shielding effect for all carbon atoms of the pyrazoline moiety, only C-3 was negligibly deshielded. In the ¹H NMR spectra the 5-membered heterocyclic derivatives are observed as

ABX type spin system pattern. Observed downfield chemical shift values of all the pyrrolidinone carbon atoms and the 4''-COOH carbon were caused by the interactions of the unsubstituted NH hydrogen with CO groups.

The spectra of the 5-membered heterocycles in compounds **5a-c** and **6a-c** changed significantly when substituents COCH₃ and Ph are attached in position 5. The substituent COCH₃ influenced C-1, C-2 and C-3 atoms about - 4.2 ppm, 1.4 ppm and 5.3 ppm respectively. By the ascendancy of the substituent Ph the atoms of 5-membered heterocycle C-1 and C-3 is shifted upfield about - 0.6 ppm and 4.1 ppm, C-2 - downfield up to 2.8 ppm.

The 5-membered heterocycle pyrazole in compounds **7a,b** is characteristically influenced by phenyl substituents. The C-3 atom is found about 144.0 ppm, as in case of compounds **6a-c**, while C-1 and C-2 are observed at ~ 150.5 ppm and ~ 104.9 ppm.

The average increments of the pyrazoline and the pyrazole for aromatic carbon atoms in 1,3,5-positions (A, B, C benzene rings) as for monosubstituted benzene rings were determined after assignment of all carbons of the studied compounds (Table 1). Values of the influences of CH=CH-CO fragment for **A** and **B** monosubstituted aromatic rings found in literature were verified. The increments of the pyrrolidinone ring, used in this calculation were found in previous our work.^[34]

Table 1. The average increments of pyrazoline and pyrazole for chemical shifts of monosubstituted benzene carbons of the studied compounds

Benzene ring	Substitution	Class of compounds				
		3	4	5	6	7
A ring	C- <i>i</i>	6.7	14.4	14.2	14.3	1.5
	C- <i>o</i>	0.8	-1.6	-2.4	-1.8	0.2
	C- <i>m</i>	0.3	-0.3	-0.1	0.2	-0.1
	C- <i>p</i>	1.6	-1.4	-1.4	-1.3	-0.2
B ring	C- <i>i</i>	8.8	3.6	2.4	3.8	3.7
	C- <i>o</i>	0.9	-2.8	-1.4	-2.4	-3.0
	C- <i>m</i>	-0.9	-0.5	-0.4	-0.1	-0.0
	C- <i>p</i>	4.3	0.1	1.5	0.3	-0.3
C ring	C- <i>i</i>	-	-	-	18.4	11.3
	C- <i>o</i>	-	-	-	-15.6	-3.2
	C- <i>m</i>	-	-	-	0.4	0.6
	C- <i>p</i>	-	-	-	-9.8	-0.1

Investigation of molecular structure of the studied compounds by the computer molecular modeling showed that all molecules are near to planar. Calculated Hückel charges successfully followed the chemical shifts of the studied compounds in ¹³C NMR spectra (Table 2).

The charge allocation obtained by MM2 method for the optimized molecules models of studied compounds afforded ground for calculating the π -bond orders other than 1, 1.5, 2. The analysis of this computation showed the formation of the wide-ranging extended π -system in the molecules of compounds **3a-c**, **7a,b** (Table 3).

Table 2. ^{13}C NMR chemical shifts of C-1, C-2, C-3 atoms of compounds **3a-c**, **5a-c** and corresponding Hückel charges

Compound	Carbon atom	a	b	c
3	C-1	143.2 / 0.053	143.0 / 0.054	142.2 / 0.047
	C-2	121.9 / -0.093	119.4 / -0.126	122.7 / -0.129
	C-3	187.7 / 0.398	187.5 / 0.392	187.5 / 0.386
5	C-1	59.4 / 0.043	58.9 / 0.042	58.8 / 0.042
	C-2	42.1 / -0.090	42.1 / -0.094	41.9 / -0.096
	C-3	153.7 / 0.083	153.7 / 0.084	153.7 / 0.085

Table 3. π -Bond order, computed from molecular models of compounds **3a** and **7a**

Bonds	3a	7a
C(1') – C(1)	1.272	1.164
C(1) – C(2)	1.924	1.729
C(2) – C(3)	1.261	1.580
C(3) – C(4)	1.224	1.245
N(4) – N(5)	-	1.373
N(5) – C(10)	-	1.277
C(3) – N(4)	-	1.700
C(7) – N(1)	1.278	1.268
N(1) – C(2'')	1.454	1.456
C(2'') – O	1.796	1.794
C(2'') – C(3'')	1.000	1.000
N(1) – C(5'')	1.000	1.000

Experimental Section

General Procedures. The ^1H and ^{13}C spectra were recorded on a *Varian Unity Inova* (300 MHz) spectrometer operating in the Fourier transform mode. Chemical shifts (δ) are given from TMS (0.0 ppm) as an internal standard for ^1H NMR, and d_6 -DMSO (39.5 ppm) for ^{13}C NMR. Melting points were determined on an automatic APA1 melting point apparatus and are uncorrected. The IR spectra were determined in potassium bromide pellets on a Perkin – Elmer FT-IR system

spectrum GX spectrometer. Mass spectra were obtained on a Waters (Micromass) ZQ 2000 spectrometer using chemical ionization (CI) mode. Elemental analyses were performed on a CE-440 elemental analyser.

The molecular modeling of the study compounds was carried out using Chem 3D Ultra 9.0 (Licence Cambridge Software Package, Serial number: 031 406391 4800).

1-(4-Acetylphenyl)-4-carboxy-2-pyrrolidinone (2). A mixture of 67.58 g (0.5 mol) 4-aminoacetophenone **1** and 78.06 g (0.6 mol) itaconic acid in 150 ml of water was heated at reflux 15 hours, then treated with 280 ml 10% NaOH. After cooling to 20°C the reaction mixture was filtered, filtrate acidified with aq HCl to pH 1, resulting precipitate filtered, then washed with water, yield 84%; mp 170-171°C (2-propanol); IR (KBr), cm^{-1} : 3006 (OH), 1726, 1702, 1639 (C=O). MS m/z , (%): $[M+H]^+=248.5(100)$. ^1H NMR (300 MHz, d_6 -DMSO) δ : 2.57 (s, 3H, CH_3CO), 2.70-2.87 (m, 2H, CH_2CO), 3.31-3.43 (m, 1H, CH), 3.99-4.13 (m, 2H, CH_2N), 7.81, 7.96 (2d, $J=9.0$ Hz, 4H, H_{ar}), 12.86 (s, 1H, COOH). ^{13}C NMR (75 MHz, d_6 -DMSO) δ : 26.5 (COCH_3), 35.0 (C-4), 35.3 (C-3), 49.7 (C-3), 118.4 (C-2', 6'), 129.1 (C-3', 5'), 132.0 (C-4'), 143.1 (C-1'), 172.6 (COOH), 174.0 (C-2), 196.6 (COCH_3). Anal. calcd. for $\text{C}_{13}\text{H}_{13}\text{NO}_4$, (%): C 63.15, H 5.30, N 5.67; Found (%), C 62.48, H 4.89, N 5.29.

4-Carboxy-1-(4-styrylcarbonylphenyl)-2-pyrrolidinones (3a-c). General Procedure. A mixture 2.47 g (0.01 mol) 1-(4-acetylphenyl)-4-carboxy-2-pyrrolidinone **2**, 0.015 mol corresponding benzaldehyde and 15 ml 10% NaOH in 10 ml of ethanol was refluxed for 4 hours and cooled, 15 ml water was added and acidified with aq HCl to pH 1-2. The precipitate filtered, and then washed with water.

4-Carboxy-1-(4-styrylcarbonylphenyl)-2-pyrrolidinone (3a). Yield 74%, mp 208-209°C (ethanol), IR (KBr), cm^{-1} : 3446 (OH), 1726, 1694, 1660 (C=O), 1602 (CH=CH). MS m/z , (%): $[M+H]^+=336.4(100)$. ^1H NMR (300 MHz, d_6 -DMSO) δ : 2.72-2.89 (m, 2H, CH_2CO), 3.34-3.46 (m, 1H, CH), 4.03-4.17 (m, 2H, CH_2N), 7.46-7.51 (m, 3H, H_{ar}), 7.76 (d, $J=15.6$ Hz, 1H, ($\text{CH}=\text{CH}$)), 7.87-7.98 (m, 4H, H_{ar}), 7.99 (d, $J=15.6$ Hz, 1H, ($\text{CH}=\text{CH}$)), 8.23 (d, 2H, $J=8.9$ Hz, H_{ar}), 12.91 (s, 1H, COOH). ^{13}C NMR (75 MHz, d_6 -DMSO) δ : 35.1 (C-4''), 35.4 (C-3''), 49.8 (C-5''), 118.5 (C-6, 8), 121.9 (C-2), 128.9 (C-2', 6'), 128.9 (C-3', 5'), 129.5 (C-5, 9), 130.6 (C-4'), 132.7 (C-4), 134.7 (C-1'), 143.2 (C-1), 143.6 (C-7), 172.7 (COOH), 174.1 (C-2''), 187.7 (C-3). Anal. calcd. for $\text{C}_{20}\text{H}_{17}\text{NO}_4$, (%): C 71.63, H 5.11, N 4.18; Found (%), C 71.2, H 5.50, N 3.9.

4-Carboxy-1-[4-(4-methoxystyrylcarbonyl)phenyl]-2-pyrrolidinone (3b). Yield 71%, mp 197-198°C (ethanol), IR (KBr), cm^{-1} : 3341 (OH), 1731, 1711, 1652 (C=O), 1593 (CH=CH). MS m/z , (%): $[M+H]^+=366.4(100)$. ^1H NMR (300 MHz, d_6 -DMSO) δ : 2.72-2.90 (m, 2H, CH_2CO), 3.34-3.44 (m, 1H, CH), 3.82 (s, 3H, OCH_3), 4.02-4.16 (m, 2H, CH_2N), 7.02 (d, $J=8.8$ Hz, 2H, H_{ar}), 7.70 (d, $J=15.5$ Hz, 1H, ($\text{CH}=\text{CH}$)), 7.82 (d, $J=15.5$ Hz, 1H, ($\text{CH}=\text{CH}$)), 7.85 (d, $J=9.0$ Hz, 2H, H_{ar}), 7.86 (d, $J=8.8$ Hz, 2H, H_{ar}), 8.18 (d, $J=9.0$ Hz, 2H, H_{ar}), 12.89 (s, 1H, COOH). ^{13}C NMR (75 MHz, d_6 -DMSO) δ : 35.1 (C-4''), 35.4 (C-3''), 49.8 (C-5''), 55.4 (OCH_3), 114.4 (C-3', 5'), 118.5 (C-6, 8), 119.4 (C-2), 127.4 (C-1'), 129.5 (C-5, 9), 130.8 (C-2', 6'), 133.0 (C-4), 143.0

(C-1), 143.6 (C-7), 161.3 (C-4'), 174.1 (C-2''), 172.6 (COOH), 187.5 (C-3). Anal. calcd. for C₂₁H₁₉NO₅, (%): C 69.03, H 5.24, N 3.83; Found (%), C 65.9, H 5.17, N 3.70.

1-[4-(4-Bromostyrylcarbonyl)phenyl]-4-carboxy-2-pyrrolidinone (3c). Yield 78%, mp 243-244°C (dioxane), IR (KBr), cm⁻¹: 3457 (OH), 1732, 1661, 1607 (C=O), 1595 (CH=CH). MS m/z, (%): [M+H]⁺=414.3(98), [M+H+2]⁺=416.3(100). ¹H NMR (300 MHz, d₆-DMSO) δ: 2.72-2.90 (m, 2H, CH₂CO), 3.34-3.44 (m, 1H, CH), 4.03-4.17 (m, 2H, CH₂N), 7.65 (d, *J*=8.5 Hz, 2H, H_{ar}), 7.69 (d, *J*=15.7 Hz, 1H, (CH=CH)), 7.85, (d, *J*=8.9 Hz, 2H, H_{ar}), 7.86 (d, 2H, *J*=8.5 Hz, H_{ar}), 7.98 (d, *J*=15.7 Hz, 1H, (CH=CH)), 8.19 (d, *J*=8.9 Hz, 2H, H_{ar}), 12.85 (s, 1H, COOH). ¹³C NMR (75 MHz, d₆-DMSO) δ: 35.0 (C-4''), 35.4 (C-3''), 49.8 (C-5''), 118.5 (C-6, 8), 122.7 (C-2), 123.9 (C-4'), 132.6 (C-4), 129.7 (C-5, 9), 130.8 (C-2', 6'), 131.9 (C-3', 5'), 134.0 (C-1'), 142.2 (C-1), 143.3 (C-7), 174.1 (C-2''), 172.7 (COOH), 187.5 (C-3). Anal. calcd. for C₂₀H₁₆BrNO₄, (%): C 57.99, H 3.89, N 3.38; Found (%), C 57.62, H 2.96, N 3.45.

1-[4-(5-Aryl-4,5-dihydro-1H-pyrazol-3-yl)phenyl]-5-oxopyrrolidine-3-carboxylic acids (4a-c). General Procedure. A solution of 0.002 mol of the corresponding chalcones **3a-c**, 0.3 g (0.006 mol) of hydrazine hydrate (concentration 99%) and 10 ml of ethanol was refluxed for 5 hours and cooled. The precipitate filtered, and then washed with ethanol and diethyl ether.

5-Oxo-1-[4-(5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)phenyl]pyrrolidine-3-carboxylic acid (4a). Yield 81%; mp 171-172°C (ethanol), IR (KBr), cm⁻¹: 3419 (OH), 3346 (NH), 1679, 1654 (C=O), 1606 (C=N). MS m/z, (%): [M+H]⁺=350.3(100). ¹H NMR (300 MHz, d₆-DMSO) δ: 2.62-2.79 (m, 2H, CH₂CO), 2.82 (dd, *J*=10.7 Hz, *J*=16.3 Hz, 1H, CH₂(C-2)), 2.94-3.04 (m, 1H, CH_{pyrrolid.}), 3.43 (dd, *J*=10.7 Hz, *J*=16.3 Hz, 1H, CH₂(C-2)), 3.93-4.03 (m, 2H, CH₂N), 4.82 (t, *J*=10.7 Hz, 1H, CH(C-1)), 7.23-7.45 (m, 5H, H_{ar} +NH), 7.61, 7.69 (2d, *J*=9.0 Hz, 4H, H_{ar}). ¹³C NMR (75 MHz, d₆-DMSO) δ: 36.8 (C-4''), 37.2 (C-3''), 40.6 (C-2), 51.5 (C-5''), 63.7 (C-1), 118.9 (C-6, 8), 125.8 (C-5, 9), 126.6 (C-2', 6'), 127.1 (C-4), 128.4 (C-3', 5'), 128.5 (C-4'), 139.4 (C-7), 143.0 (C-1'), 148.3 (C-3), 173.4 (COOH), 176.3 (C-2''). Anal. calcd. for C₂₀H₁₉N₃O₃, (%): C 68.75, H 5.48, N 12.03; Found (%), C 68.36, H 5.51, N 11.78.

1-[4-[5-(4-Methoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl]phenyl]-5-oxopyrrolidine-3-carboxylic acid (4b). Yield 87%, mp 174-175°C (ethanol), IR (KBr), cm⁻¹: 3436 (OH), 3352 (NH), 1677, 1658 (C=O), 1607 (C=N). MS m/z, (%): [M+H]⁺=380.3(100). ¹H NMR (300 MHz, d₆-DMSO) δ: 2.62-2.78 (m, 2H, CH₂CO), 2.79 (dd, *J*=10.7 Hz, *J*=16.2 Hz, 1H, CH₂(C-2)), 3.00-3.10 (m, 1H, CH_{pyrrolid.}), 3.38 (dd, *J*=10.5 Hz, *J*=16.2 Hz, 1H, CH₂(C-2)), 3.73 (s, 3H, OCH₃), 3.93-4.03 (m, 2H, CH₂N), 4.77 (t, *J*=10.7 Hz, 1H, CH (C-1)), 6.90, 7.29 (2d, *J*=8.8 Hz, 4H, H_{ar}), 7.42 (br. s, 1H, NH), 7.60, 7.68 (2d, *J*=9.0 Hz, 4H, H_{ar}). ¹³C NMR (75 MHz, d₆-DMSO) δ: 36.5 (C-4''), 36.8 (C-3''), 40.6 (C-2), 51.2 (C-5''), 55.1 (OCH₃), 63.2 (C-1), 113.7 (C-3', 5'), 118.9 (C-6, 8), 125.7 (C-5, 9), 127.8 (C-2', 6'), 128.7 (C-4), 134.9 (C-1'), 139.3 (C-7), 148.4 (C-3), 158.4 (C-4'), 175.7 (C-2''), 173.1 (COOH). Anal. calcd. for C₂₁H₂₁N₃O₄, (%): C 66.48, H 5.58, N 11.07; Found (%), C 66.12, H 5.29, N 11.25.

1-[4-[5-(4-Bromophenyl)-4,5-dihydro-1H-pyrazol-3-yl]phenyl]-5-oxopyrrolidine-3-carboxylic acid (4c). Yield 72%, mp 167-168°C (ethanol), IR (KBr), cm⁻¹: 3446 (OH), 3320 (NH),

1694, 1682 (C=O), 1604 (C=N). MS m/z , (%): $[M+H]^+=428.2(100)$; $[M+H+2]^+=430.2(70)$. 1H NMR (300 MHz, d_6 -DMSO) δ : 2.69-2.78 (m, 2H, CH_2CO), 2.80 (dd, $J=9.0$ Hz, $J=14.4$ Hz, 1H, $CH_2(C-2)$), 3.20-3.31 (m, 1H, $CH_{pyrrolid.}$), 3.44 (dd, $J=10.6$ Hz, $J=16.4$ Hz, 1H, $CH_2(C-2)$), 3.95-4.11 (m, 2H, CH_2N), 4.83 (t, $J=10.6$ Hz, 1H, $CH(C-1)$), 7.18-7.94 (m, 8H, H_{ar}). ^{13}C NMR (75 MHz, d_6 -DMSO) δ : 35.7 (C-4''), 35.7 (C-3''), 40.5 (C-2), 51.2 (C-5''), 62.9 (C-1), 119.1 (C-6, 8), 120.1 (C-4'), 125.8 (C-5, 9), 127.1 (C-4), 128.9 (C-2', 6'), 131.2 (C-3', 5'), 139.1 (C-7), 142.5 (C-1'), 148.4 (C-3), 173.4 (COOH), 174.7 (C-2''). Anal. calcd. for $C_{20}H_{18}BrN_3O_3$, (%): C 56.09, H 4.24, N 9.81; Found (%), C 56.23, H 3.96, N 10.06.

1-[4-(1-Acetyl-5-aryl-4,5-dihydro-1H-pyrazol-3-yl)phenyl]-5-oxopyrrolidine-3-carboxylic acids (5a-c). General Procedure. A solution of 0.002 mol of the corresponding chalcones **3a-c**, 0.3 g (0.006 mol) of hydrazine hydrate and 10 ml of acetic acid was refluxed for 5 hours, then catalytic amount of HCl (4-5 drops) was added and yet refluxed for 30 min. After cooling 30 ml water was added and the resulting precipitate was filtered, washed with water.

1-[4-(1-Acetyl-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)phenyl]-5-oxopyrrolidine-3-carboxylic acid (5a). Yield 56%, mp 247-248°C (ethanol), IR (KBr), cm^{-1} : 3448 (OH), 1730, 1706, 1655 (C=O), 1607 (C=N). MS m/z , (%): $[M+H]^+=392.4(100)$. 1H NMR (300 MHz, d_6 -DMSO) δ : 2.31 (s, 3H, $COCH_3$), 2.69-2.87 (m, 2H, CH_2CO), 3.11 (dd, $J=4.5$ Hz, $J=18.0$ Hz, 1H, $CH_2(C-2)$), 3.31-3.42 (m, 1H, $CH_{pyrrolid.}$), 3.84 (dd, $J=11.8$ Hz, $J=18.0$ Hz, 1H, $CH_2(C-2)$), 3.98-4.13 (m, 2H, CH_2N), 5.53 (dd, $J=4.5$ Hz, $J=11.8$ Hz, 1H, $CH(C-1)$), 7.17-7.99 (m, 10H, $H_{ar} + NH$), 12.83 (br. s, 1H, COOH). ^{13}C NMR (75 MHz, d_6 -DMSO) δ : 21.7 ($COCH_3$), 35.1 (C4''), 35.4 (C-3''), 42.1 (C-2), 49.9 (C-5''), 59.4 (C-1), 119.1 (C-6, 8), 125.4 (C-2', 6'), 126.4 (C-4), 127.2 (C-5, 9), 128.6 (C-3', 5'), 128.8 (C-4'), 140.7 (C-7), 142.5 (C-1'), 153.7 (C-3), 167.3 ($COCH_3$), 172.2 (COOH), 174.1 (C-2''). Anal. calcd. for $C_{22}H_{21}N_3O_4$, (%): C 67.51, H 5.41, N 10.74; Found (%), C 67.45, H 5.57, N 10.53.

1-[4-[1-Acetyl-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl]phenyl]-5-oxopyrrolidine-3-carboxylic acid (5b). Yield 84%, mp 213-214°C (2-propanol), IR (KBr), cm^{-1} : 3431 (OH), 1702, 1654, 1639 (C=O), 1608 (C=N). MS m/z , (%): $[M+H]^+=422.4(100)$. 1H NMR (300 MHz, d_6 -DMSO) δ : 2.28 (s, 3H, $COCH_3$), 2.70-2.86 (m, CH_2CO), 3.10 (dd, 1H, $J=4.5$ Hz, $J=18.0$ Hz, 1H, $CH_2(C-2)$); 3.30-3.40 (m, 1H, $CH_{pyrrolid.}$), 3.10 (s, 3H, OCH_3), 3.80 (dd, $J=11.7$ Hz, $J=18.0$ Hz, 1H, $CH_2(C-2)$), 3.95-4.11 (m, 2H, CH_2N), 5.48 (dd, $J=4.5$ Hz, $J=11.7$ Hz, $CH(C-1)$), 6.87, 7.10 (2d, $J=8.8$ Hz, 4H, H_{ar}), 7.77 (s, 4H, H_{ar}), 11.98 (br. s, 1H, COOH). ^{13}C NMR (75 MHz, d_6 -DMSO) δ : 21.8 ($COCH_3$), 35.2 (C-4''), 35.4 (C-3''), 50.0 (C-5''), 42.1 (C-2), 55.1 (OCH_3), 58.9 (C-1), 114.0 (C-3', 5'), 119.0 (C-6, 8), 126.5 (C-4), 126.8 (C-5, 9), 127.2 (C-2', 6'), 134.5 (C-1'), 140.7 (C-7), 153.7 (C-3), 158.4 (C-4'), 167.2 ($COCH_3$), 172.4 (COOH), 174.3 (C-2''). Anal. calcd. for $C_{23}H_{23}N_3O_5$, (%): C 65.55, H 5.50, N 9.97; Found (%), C 65.29, H 5.22, N 10.21.

1-[4-[1-Acetyl-5-(4-bromophenyl)-4,5-dihydro-1H-pyrazol-3-yl]phenyl]-5-oxopyrrolidine-3-carboxylic acid (5c). Yield 88%, mp 262-263°C (2-propanol), IR (KBr), cm^{-1} : 3440 (OH), 1704, 1662, 1652 (C=O), 1607 (C=N). MS m/z , (%): $[M+H]^+=470.2(98)$, $[M+H+2]^+=472.2(100)$. 1H NMR (300 MHz, d_6 -DMSO) δ : 2.30 (s, 3H, $COCH_3$), 2.68-2.86 (m,

2H, CH₂CO), 3.13 (dd, $J=4.7$ Hz, $J=18.1$ Hz, 1H, CH₂(C-2)), 3.30-3.41 (m, 1H, CH_{pyrrolid.}), 3.83 (dd, $J=11.8$ Hz, $J=18.1$ Hz, 1H, CH₂(C-2)), 3.97-4.11 (m, 2H, CH₂N), 5.55 (dd, $J=4.7$ Hz, $J=11.8$ Hz, CH (C-1)), 7.15, 7.55 (2d, $J=8.5$ Hz, 4H, H_{ar}), 7.17 (s, 4H, H_{ar}), 12.94 (br. s, 1H, COOH). ¹³C NMR (75 MHz, d₆-DMSO) δ : 21.7 (COCH₃), 35.1 (C-4''), 35.4 (C-3''), 41.9 (C-2), 49.9 (C-5''), 58.8 (C-1), 119.0 (C-6, 8), 120.2 (C-4'), 126.3 (C-4), 127.3 (C-5, 9), 127.9 (C-2', 6'), 131.5 (C-3', 5'), 140.8 (C-7), 141.8 (C-1'), 153.7 (C-3), 167.4 (COCH₃), 174.3 (C-2''), 172.3 (COOH). Anal. calcd. for C₂₂H₂₀BrN₃O₄, (%): C 56.18, H 4.29, N 8.93; Found (%), C 55.97, H 4.69, N 9.02.

1-[4-(1,5-Diaryl-4,5-dihydro-1H-pyrazol-3-yl)phenyl]-5-oxopyrrolidine-3-carboxylic acids (6a-c). General Procedure. A solution of 0.003 mol of the corresponding chalcones **3a-c**, 0.43 g (0.004 mol) of phenylhydrazine and 10 ml of 1,4-dioxane was refluxed for 4 hours, when catalytic amount of HCl (4-5 drops) was added and yet refluxed for 30 min. After cooling 50 ml water was added and the resulting precipitate was filtered, washed with water. Purified by the repeated twice precipitation from 10% Na₂CO₃ solution with acetic acid.

5-Oxo-1-[4-(1,5-diphenyl-4,5-dihydro-1H-pyrazol-3-yl)phenyl]pyrrolidine-3-carboxylic acid (6a). Yield 77%, mp 160-161°C (ethanol), IR (KBr), cm⁻¹: 3436 (OH), 1733, 1705 (C=O), 1613 (C=N). MS m/z, (%): [M+H]⁺=426.5(100). ¹H NMR (300 MHz, d₆-DMSO) δ : 2.74 (br. s, 2H, CH₂CO), 3.06 (dd, $J=6.2$, $J=17.5$, 1H, CH₂(C-2)), 3.01 (br. s, 1H, CH_{pyrrolid.}), 3.86 (dd, $J=12.0$ Hz, $J=17.5$ Hz, 1H, CH₂(C-2)), 4.01 (br. s, 2H, CH₂N), 5.41 (dd, 1H, $J=6.2$ Hz, $J=12.0$ Hz, CH(C-1)), 6.67-7.92 (m, 14H, H_{ar}). ¹³C NMR (75 MHz, d₆-DMSO) δ : 35.2 (C-4''), 36.2 (C-3''), 43.6 (C-2), 50.6 (C-5''), 55.2 (OCH₃), 63.1 (C-1), 112.9 (C-11, 15), 119.0 (C-13), 119.5 (C-6, 8), 127.8 (C-4), 126.2 (C-5, 9), 127.4 (C-2', 6'), 128.6 (C-4'), 128.6 (C-3', 5'), 129.0 (C-12, 14), 139.6 (C-7), 142.6 (C-1'), 144.3 (C-3), 147.0 (C-10), 171.9 (COOH), 174.7 (C-2''). Anal. calcd. for C₂₆H₂₃N₃O₃, (%): C 73.4, H 5.45, N 9.88; Found (%), C 73.58, H 5.47, N 9.62.

1-{4-[5-(4-Methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl]phenyl}-5-oxopyrrolidine-3-carboxylic acid (6b). Yield 48%, mp 139-140°C (ethanol), IR (KBr), cm⁻¹: 2931 (OH), 1734, 1703 (C=O), 1598 (C=N). MS m/z, (%): [M+H]⁺= 456.3(100). ¹H NMR (300 MHz, d₆-DMSO) δ : 2.68-2.86 (m, 2H, CH₂CO), 3.06 (dd, $J=6.4$ Hz, $J=17.4$ Hz, 1H, CH₂(C-2)), 3.33-3.42 (m, 1H, CH_{pyrrolid.}), 3.71 (s, 3H, OCH₃), 3.86 (dd, $J=12.0$ Hz, $J=17.4$ Hz, 1H, CH₂(C-2)), 3.97-4.11 (m, 2H, CH₂N), 5.40 (dd, $J=6.4$ Hz, $J=12.0$ Hz, 1H, CH(C-1)), 6.70 (t, $J=7.3$ Hz, 1H, H_{ar}), 6.89 (d, $J=8.6$ Hz, 2H, H_{ar}), 7.00 (d, $J=7.8$ Hz, 2H, H_{ar}), 7.14 (dd, $J=7.3$ Hz, $J=7.8$ Hz, 2H, H_{ar}), 7.21 (d, $J=8.6$ Hz, 2H, H_{ar}), 7.73 (s, 4H, H_{ar}), 12.79 (br. s. COOH). ¹³C NMR (75 MHz, d₆-DMSO) δ : 35.1 (C-4''), 35.3 (C-3''), 43.0 (C-2), 49.9 (C-5''), 55.0 (OCH₃), 62.6 (C-1), 113.0 (C-11, 15), 114.3 (C-3', 5'), 118.4 (C-13), 119.2 (C-6, 8), 126.1 (C-5, 9), 127.1 (C-2', 6'), 127.9 (C-4), 128.6 (C-4'), 128.8 (C-12, 14), 134.4 (C-1'), 139.4 (C-7), 144.3 (C-3), 146.8 (C-10), 158.4 (C-4'), 172.0 (COOH), 174.2 (C-2''). Anal. calcd. for C₂₇H₂₅N₃O₄, (%): C 71.19, H 5.53, N 9.22; Found (%), C 70.81, H 5.87, N 9.51.

1-{4-[5-(4-Bromophenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl]phenyl}-5-oxopyrrolidine-3-carboxylic acid (6c). Yield 65%, mp 152-153°C (ethanol), IR (KBr), cm⁻¹: 3027 (OH), 1705,

1675 (C=O), 1598 (C=N). MS m/z , (%): $[M+H]^+=504.3(100)$, $[M+H+2]^+=506.3(98)$. 1H NMR (300 MHz, d_6 -DMSO) δ : 2.69-2.86 (m, 2H, CH_2CO), 3.10 (dd, $J=6.3$ Hz, $J=17.5$ Hz, 1H, $CH_2(C-2)$), 3.32-3.42 (m, 1H, $CH_{pyrrolid.}$), 3.89 (dd, $J=12.1$ Hz, $J=17.5$ Hz, 1H, $CH_2(C-2)$), 3.98-4.11 (m, 2H, CH_2N), 5.49 (dd, $J=6.3$ Hz, $J=12.1$ Hz, 1H, CH (C-1)), 6.73 (t, $J=7.3$ Hz, 1H, H_{ar}), 6.98 (d, $J=8.5$ Hz, 2H, H_{ar}), 7.16 (dd, $J=7.3$ Hz, $J=8.5$ Hz, 2H, H_{ar}), 7.25 (d, $J=8.5$ Hz, 2H, H_{ar}), 7.53 (d, $J=8.5$ Hz, 2H, H_{ar}), 7.74 (s, 4H, H_{ar}), 12.91 (br. s, 1H, COOH). ^{13}C NMR (75 MHz, d_6 -DMSO) δ : 35.1 (C-4''), 35.3 (C-3''), 42.7 (C-2), 49.9 (C-5''), 62.4 (C-1), 112.9 (C-11, 15), 118.7 (C-13), 119.2 (C-6, 8), 120.4 (C-4'), 126.2 (C-5, 9), 127.7 (C-4), 128.2 (C-2', 6'), 129.0 (C-12, 14), 131.9 (C-3', 5'), 139.5 (C-7), 141.9 (C-1'), 144.0 (C-3), 147.0 (C-10), 172.1 (COOH), 174.2 (C-2''). Anal. calcd. for $C_{26}H_{22}BrN_3O_3$, (%): C 61.91, H 4.40, N 8.33; Found (%), C 62.03, H 4.21, N 8.39.

1-[4-(1,5-Diaryl-1H-pyrazol-3-yl)phenyl]-5-oxopyrrolidine-3-carboxylic acids (7a,b).

General Procedure. A solution of 0.003 mol of the corresponding chalcones **3a-c**, 0.43 g (0.004 mol) of phenylhydrazine and 10 ml of acetic acid was refluxed for 4 hours, when catalytic amount of HCl (4-5 drops) was added and yet refluxed for 30 min. After cooling 50 ml water was added and the resulting precipitate was filtered, washed with water. Purified by the repeated twice precipitation from 10% Na_2CO_3 solution with acetic acid.

5-Oxo-1-[4-(1,5-diphenyl-1H-pyrazol-3-yl)phenyl]pyrrolidine-3-carboxylic acid (7a). Yield 65%, mp 135-136°C (acetone), IR (KBr), cm^{-1} : 2908 (OH), 1746, 1661, (C=O), 1609 (C=CH), 1597 (C=N). MS m/z , (%): $[M+H]^+=423.5(100)$. 1H NMR (300 MHz, d_6 -DMSO) δ : 2.72-2.89 (m, 2H, CH_2CO), 3.35-3.45 (m, 1H, $CH_{pyrrolid.}$), 4.02-4.15 (m, 2H, CH_2N), 7.17 (s, 1H, CH (C-2)), 7.29-7.48 (m, 10H, H_{ar}), 7.78, 7.95 (2d, $J=8.8$ Hz, 4H, H_{ar}), 12.89 (br. s, 1H, COOH). ^{13}C NMR (75 MHz, d_6 -DMSO) δ : 35.1 (C-4''), 35.3 (C-3''), 49.9 (C-5''), 104.2 (C-2), 119.4 (C-6, 8), 125.2 (C-11, 15), 125.7 (C-5, 9), 127.7 (C-4), 128.3 (C-13), 129.3 (C-4'), 128.4 (C-3', 5'), 128.6 (C-2', 6'), 129.1 (C-12,14), 123.0 (C-1'), 138.9 (C-7), 139.8 (C-10), 144.1 (C-3), 150.5 (C-1), 171.9 (COOH), 174.2 (C-2''). Anal. calcd. for $C_{26}H_{21}N_3O_3$, (%): C 73.74, H 5.00, N 9.92; Found (%), C 73.89, H 4.87, N 9.82.

1-[4-[5-(4-Methoxyphenyl)-1-phenyl-1H-pyrazol-3-yl]phenyl]-5-oxopyrrolidine-3-carboxylic acid (7b). Yield 65%, mp 115-116°C (ethanol), IR (KBr), cm^{-1} : 3053 (OH), 1706, 1656 (C=O), 1613 (C=CH), 1598 (C=N). MS m/z , (%): $[M+H]^+=454.5(100)$. 1H NMR (300 MHz, d_6 -DMSO) δ : 2.69-2.87 (m, 2H, CH_2CO), 3.28-3.43 (m, 1H, $CH_{pyrrolid.}$), 3.76 (s, 3H, OCH_3), 4.00-4.14 (m, 2H, CH_2N), 6.94 (d, $J=8.9$ Hz, 2H, H_{ar}), 7.07 (s, 1H, CH (C-2)), 7.22 (d, $J=8.9$ Hz, 2H, H_{ar}), 7.32-7.47 (m, 5H, H_{ar}), 7.75, 7.92 (2d, $J=8.9$ Hz, 4H, H_{ar}), 12.85 (br. s, 1H, COOH). ^{13}C NMR (75 MHz, d_6 -DMSO) δ : 35.1 (C-4''), 35.3 (C-3''), 49.9 (C-5''), 55.2 (OCH_3), 104.7 (C-2), 114.1 (C-3', 5'), 119.4 (C-6, 8), 120.1 (C-12, 14), 122.2 (C-1'), 125.2 (C-11, 15), 125.6 (C-5, 9), 127.6 (C-4), 128.4 (C-13), 129.8 (C-2', 6'), 139.9 (C-10), 144.0 (C-3), 150.4 (C-1), 159.3 (C-4'), 171.9 (COOH), 174.2 (C-2''). Anal. calcd. for $C_{27}H_{23}N_3O_4$, (%): C 71.51, H 5.11, N 9.27; Found (%), C 71.64, H 5.36, N 8.99.

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