Synthesis of carboxylic acid derivatives of 2-pyrazolines

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Abstract

2-Pyrazolines **7-12** bearing a carboxylic acid ester or a carboxamide side-chain have been prepared by treatment of the appropriate chalcone derivatives **2-6** with hydrazine hydrate or phenylhydrazine in hot acetic acid. 1-(2-Carboxyphenyl)-2-pyrazolines **24-30** and 1-(4-carboxyphenyl)-2-pyrazolines **31-41** were synthesized by the reaction of chalcones with (2-carboxyphenyl)hydrazine and (4-carboxyphenyl)hydrazine in hot acetic acid. Structures of all new compounds have been elucidated by microanalyses, ^{1}H-, ^{13}C-NMR and IR spectroscopic measurements.

Keywords: Chalcones, hydrazines, 2-pyrazolines

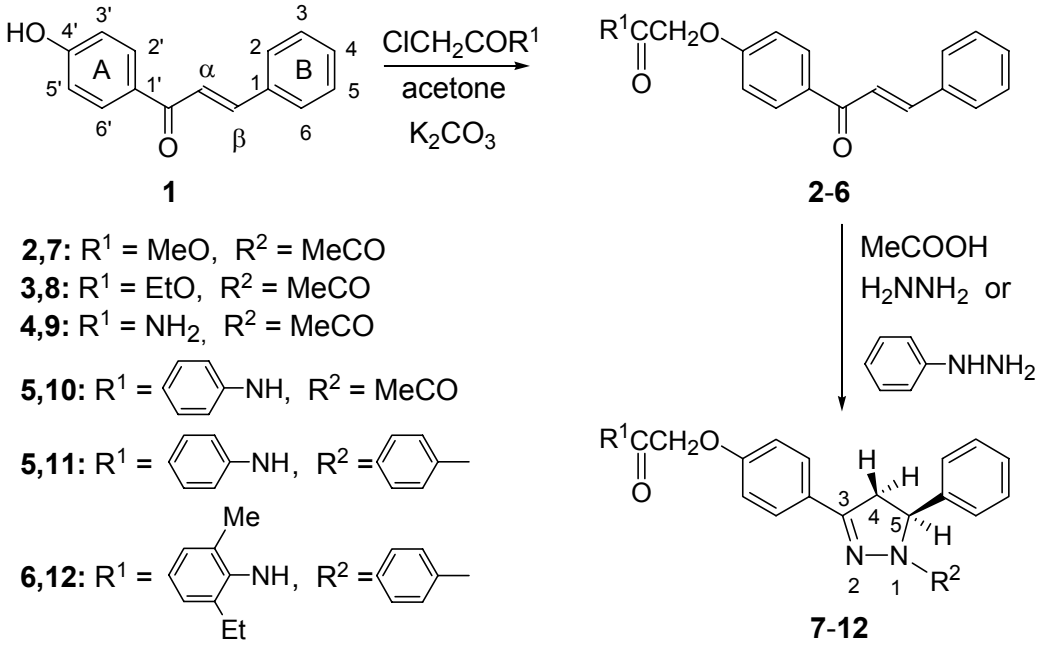
Introduction

Pyrazolines are well known nitrogen-containing heterocyclic compounds and several procedures have been developed for their synthesis.[1-3] Numerous pyrazolines have been found to possess important bioactivities, *viz.* central nervous system,[4] antimicrobial and antimycotic,[5,6] immunosuppressive,[7] *etc.* activities. As far as the different pyrazoline isomers are concerned, 2-pyrazoline derivatives became the most frequently studied pyrazolines. Various methods are used for the preparation of 2-pyrazolines. Treatment of α,β-unsaturated aldehydes and ketones with hydrazines seems to be the most popular procedure for this purpose. This reaction has been conducted under various conditions.[8-42] As a hydrazine reagent, hydrazine hydrate or phenylhydrazine were used almost in all cases. Utilization of *p*-sulfamylphenylhydrazine is mentioned to prepare *N*-(*p*-sulfamylphenyl)-2-pyrazolines only in few cases.[43,44] In our previous paper,[40] use of (2-carboxyphenyl)hydrazine and (4-carboxypehnyl)hydrazine has been described for the synthesis of carboxylated styryl-2-pyrazolines.

As mentioned, 2-pyrazolines possess valuable bioactivities which stimulated the preparation of their numerous derivatives. Insertion of carboxy, carboxamide or carboxylic acid ester group into 2-pyrazoline molecules may be beneficial to their bioactivities. Taking this expected effect into consideration, herein we report on the preparation of new carboxylic acid derivatives of 2-pyrazolines.

Results and Discussion

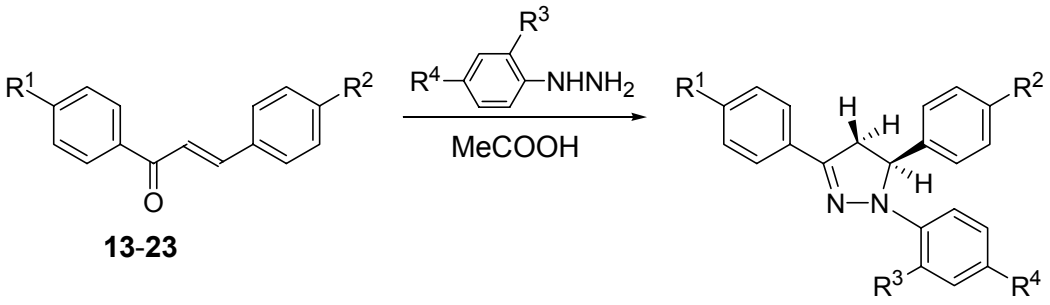
One of the aims of our present study was to synthesize new 2-pyrazolines with a carboxylic acid type side-chain. The planned side-chain was introduced into the chalcone molecules used as starting materials. For this purpose, 4'-hydroxychalcone (**1**) was allowed to react with the appropriate chloroacetic acid derivative in hot anhydrous acetone in the presence of potassium carbonate to afford chalcones **2-6** (Scheme 1). Previously, acetic acid was found to be a convenient and cheap solvent for the synthesis of a wide variety of 2-pyrazolines by the reaction of α,β-unsaturated ketones and hydrazines.[9,33-42] For this reason, chalcones **2-6** were allowed to react either with hydrazine hydrate or with phenylhydrazine to obtain 2-pyrazolines **7-12** (Scheme 1) in good (62-89%) yields. These new 1-substituted 2-pyrazolines bear either a carboxylic acid ester or a carboxamide side-chain.



Scheme 1

In case chalcones **13, 16-18** and **20-22** were treated with (2-carboxyphenyl)hydrazine in hot acetic acid 1-(2-carboxyphenyl)-2-pyrazolines **24-30** (Scheme 2) were prepared in medium to

good (58-65%) yields. This is the first example for the reaction of chalcones with (2-carboxyphenyl)hydrazine to form carboxylated 2-pyrazoline derivatives.



13-23 **24-41**

13,24: $R^1 = R^2 = R^4 = H$, $R^3 = COOH$
16,25: $R^1 = F$, $R^2 = R^4 = H$, $R^3 = COOH$
17,26: $R^1 = Cl$, $R^2 = R^4 = H$, $R^3 = COOH$
18,27: $R^1 = Br$, $R^2 = R^4 = H$, $R^3 = COOH$
20,28: $R^1 = R^4 = H$, $R^2 = Me$, $R^3 = COOH$
21,29: $R^1 = R^4 = H$, $R^2 = Cl$, $R^3 = COOH$
22,30: $R^1 = R^4 = H$, $R^2 = Br$, $R^3 = COOH$
13,31: $R^1 = R^2 = R^3 = H$, $R^4 = COOH$
14,32: $R^1 = Me$, $R^2 = R^3 = H$, $R^4 = COOH$
15,33: $R^1 = MeO$, $R^2 = R^3 = H$, $R^4 = COOH$
16,34: $R^1 = F$, $R^2 = R^3 = H$, $R^4 = COOH$
17,35: $R^1 = Cl$, $R^2 = R^3 = H$, $R^4 = COOH$
18,36: $R^1 = Br$, $R^2 = R^3 = H$, $R^4 = COOH$
19,37: $R^1 = NO_2$, $R^2 = R^3 = H$, $R^4 = COOH$
20,38: $R^1 = R^3 = H$, $R^2 = Me$, $R^4 = COOH$
21,39: $R^1 = R^3 = H$, $R^2 = Cl$, $R^4 = COOH$
22,40: $R^1 = R^3 = H$, $R^2 = Br$, $R^4 = COOH$
23,41: $R^1 = R^3 = H$, $R^2 = NO_2$, $R^4 = COOH$

Scheme 2

Chalcones **13-23** were allowed to react with (4-carboxyphenyl)hydrazine in boiling acetic acid and 1-(4-carboxyphenyl)-2-pyrazolines **31-41** (Scheme 2) were obtained in medium to good (57-84%) yields. Our experimental results unequivocally prove that both the (2-carboxyphenyl)hydrazine and the (4-carboxyphenyl)hydrazine are convenient hydrazine derivatives for the synthesis of carboxylated 2-pyrazolines.

Structures of all new compounds have been elucidated by microanalyses, IR and NMR spectroscopic measurements. Elemental analyses unambiguously proved the elemental composition of all new compounds. In their IR spectra a characteristic C=N band was assigned between 1594 and 1605 cm^{-1} referring to a C=N double bond between the N-2 and C-3 atoms. In the ^{1}H-NMR spectra of 2-pyrazolines **7-12** and **24-41** the three hydrogen atoms attached to the C-4 and C-5 carbon atoms of the heterocyclic ring gave an ABX spin system. Measured chemical shift and coupling constant values (*cf.* Experimental Section) unequivocally prove the 2-pyrazoline structure. Owing to a strong hydrogen bond, in the case of the 1-(2-carboxyphenyl)-2-pyrazolines **24-30** no proton signal belonging to a carboxyl group could be detected. However, in the ^{1}H-NMR spectra of 1-(4-carboxyphenyl)-2-pyrazolines **31-41** a distinct singlet signal assigned to the carboxyl group was found around 12.10-12.40 ppm. ^{13}C-NMR chemical shift

values of carbon atoms C-3 (146-150 ppm), C-4 (43-44 ppm) and C-5 (62-64 ppm) corroborate the 2-pyrazoline structure deduced from the ^{1}H-NMR spectroscopic data.

In conclusion, we have synthesized hitherto unknown carboxylic acid derivatives of 2-pyrazolines which may serve as beneficial substances for drug research. Our experimental results prove that (2-carboxyphenyl)hydrazine and (4-carboxyphenyl)hydrazine are convenient reagents for the synthesis of 2-pyrazolines by treatment of α,β-unsaturated ketones with hydrazines.

Experimental Section

General Procedures. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were measured with a Bruker WP 200 SY spectrometer at 200/50 MHz in $CDCl_3$ or DMSO-d_6 (internal standard TMS, δ = 0.0 ppm) at ambient temperature (*ca* 20 ^{o}C). The IR spectra were obtained in KBr discs with a Perkin-Elmer 16 PC instrument. Elemental analyses (C, H, N) were measured in-house with a Carlo Erba 1106 EA instrument. TLC was performed on Kieselgel 60 F_{254} (Merck) layer using toluene: ethyl acetate (4:1 v/v) or 1,2-dichloroethane as eluents. Starting materials **1** and **13-23** were synthesized according to known procedures.[45-50]

General procedure for the preparation of chalcone derivatives 2-6

A mixture of 4'-hydroxychalcone (**1**, 20.0 mmoles), the appropriate chloroacetic acid derivative (25.0 mmoles), potassium carbonate (5.0 g) and anhydrous acetone (200 mL) was refluxed for 6 h, then the inorganic salts were separated by filtration and the solvent was evaporated under reduced pressure. The residue was crystallized from methanol to obtain compounds **13-17** (Scheme 1).

4'-(Methoxycarbonyl)methoxychalcone (**2**). Prepared as white needles in 81% yield, mp 109-110 ^{o}C; ^{1}H-NMR (δ,$CDCl_3$): 3.82 (3H, s, Me), 4.73 (2H, s, CH_2), 7.02-8.06 (m, 9 arom. H + H_α + H_β); ^{13}C-NMR (δ, $CDCl_3$): 52.3, 65.1, 114.4, 121.8, 128.3, 128.9, 130.3, 130.8, 132.1, 134.9, 144.2, 161.4, 168.7, 188.7; IR (cm^{-1}: 1758, 1655, 1604, 1448, 1338, 1218, 1177, 1085, 1021, 988, 837, 766, 567; Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.87; H, 5.49.

4'-(Ethoxycarbonyl)methoxychalcone (**3**). Obtained as white plates in 78% yield, mp 76-77 ^{o}C; ^{1}H-NMR (δ, $CDCl_3$): 1.34 (3H, t, J = 7.4 Hz, $CH_2C\underline{H}_3$), 4.31 (2H, q, J = 7.4 Hz, $C\underline{H}_2CH_3$), 4.73 (2H, s, CH_2), 6.98-8.08 (m, 9 arom. H + H_α + H_β); ^{13}C-NMR (δ, $CDCl_3$): 14.1, 61.5, 65.2, 114.4, 121.8, 128.3, 128.9, 130.3, 130.7, 132.0, 134.9, 144.2, 161.4, 168.2, 188.6; IR (cm^{-1}): 1763, 1657, 1604, 1448, 1419, 1340, 1206, 1182, 1088, 1037, 976, 831, 766, 697; Anal. Calcd. for $C_{19}H_{18}O_4$: C, 73.53; H, 5.84. Found: C, 73.62; H, 5.78.

4'-(Aminocarbonyl)methoxychalcone (**4**). Isolated as white plates in 74% yield, mp 191-192 ^{o}C; ^{1}H-NMR (δ, $CDCl_3$): 4.61 (2H, s, CH_2), 7.08-8.22 (m, 9 arom. H + H_α + H_β) 8.41 (2H, s, NH_2); ^{13}C-NMR (δ, $CDCl_3$): 66.6, 114.6, 121.9, 128.7, 128.8, 130.3, 130.7, 134.7, 143.1, 161.6,

169.3, 187.4; IR (cm^{-1}): 3478, 3143, 1693, 1659, 1607, 1509, 1419, 1341, 1303, 1256, 1219, 1176, 1058, 1034, 832, 765, 690; Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.66; H, 5.32; N, 5.05.

4'-(Phenylaminocarbonyl)methoxychalcone (**5**). Obtained as pale yellow needles in 83% yield, mp 160-161 ^oC; ^1H-NMR (δ, $CDCl_3$): 4.69 (2H, s, CH_2), 7.08-8.21 (m, 14 arom. H + H_α + H_β), 8.27 (1H, s, NH); ^{13}C-NMR (δ, $CDCl_3$): 67.4, 114.7, 120.2, 121.6, 125.1, 128.4, 128.9, 129.1, 130.5, 131.0, 132.7, 134.9, 136.6, 160.4, 165.4, 188.6; IR (cm^{-1}): 3405, 3058, 1686, 1655, 1603, 1534, 1500, 1446, 1341, 1308, 1244, 1224, 1190, 1061, 1034, 829, 766, 690; Anal. Calcd. for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found: C, 77.21; H, 5.41; N, 3.96.

4'-[(2-Ethyl-6-methylphenylamino)carbonyl]methoxychalcone (**6**). Prepared as pale yellow plates in 81% yield, mp 171-172 ^oC; ^1H-NMR (δ, $CDCl_3$): 1.17 (3H, t, J = 7.8 Hz, $CH_2C\underline{H}_3$), 2.26 (3H, s, Me), 2.53 (2H, q, J = 7.8 Hz, $C\underline{H}_2CH_3$), 4.79 (2H, s, CH_2), 7.10 -8.11 (m, 12 arom. H + H_α + H_β), 8.30 (1H, s, NH); ^{13}C-NMR (δ, $CDCl_3$): 14.5, 18.4, 24.9, 67.5, 114.6, 121.6. 126.5, 128.1, 128.4, 128.9, 130.5, 131.0, 131.8, 132.6, 134.9, 135.9, 141.0, 144.6, 160.6, 166.2, 188.5; IR (cm^{-1}): 3195, 3047, 1661, 1606, 1508, 1448, 1339, 1303, 1219, 1172, 1034, 981, 837, 765, 695ł; Anal. Calcd. for $C_{26}H_{25}NO_3$: C, 78.17; H, 6.31; N, 3.50. Found: C, 78.26; H, 6.26; N, 3.45.

General procedure for the synthesis of ester and carboxamide derivatives of 2-pyrazolines 7-12

A mixture of chalcone derivative (**2-6**, 5.0 mmoles), hydrazine hydrate (25.0 mmoles) or phenylhydraziene (25.0 mmoles) and acetic acid (30 mL) was heated at reflux for 4 h, then poured onto crushed ice. The precipitate was separated by filtration, washed with water, and crystallized from methanol to obtain 2-pyrazolines **7-12** (Scheme 1).

1-Acetyl-3-[4-(methoxycarbonyl-methoxy)phenyl]-5-phenyl-2-pyrazoline (**7**). Isolated as white needles in 65% yield, mp 141-142 ^oC; ^1H-NMR (δ, $CDCl_3$): 2.42 (3H, s, Me), 3.11 (1H, dd, J = 4.3, 17.6 Hz, 4-H_{trans}), 3.72 (1H, dd, J = 12.1, 17.6 Hz, 4-H_{cis}), 3.84 (3H, s, Me), 4.70 (2H, s, CH_2), 5.58 (1H, dd, J = 4.3, 12.1 Hz, 5-H), 6.92-7.71 (m. 9 arom. H); ^{13}C-NMR (δ, $CDCl_3$): 21.8, 42.3, 52.3, 59.8, 65.1, 114.8, 125.2, 125.5, 127.6, 128.2, 128.8, 141.8, 153.3, 159.3, 168.8; IR (cm^{-1}): 1670, 1605, 1548, 1517, 1445, 1326, 1251, 1178, 1058, 836, 759, 696; Anal. Calcd. for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.26; H, 5.77; N, 7.87.

1-Acetyl-3-[4-(ethoxycarbonyl-methoxy)phenyl]-5-phenyl-2-pyrazoline (**8**). Prepared as white needles in 72% yield, mp 127-128 ^oC; ^1H-NMR (δ, $CDCl_3$): 1.30 (3H, t, J = 6.8 Hz, $CH_2C\underline{H}_3$), 2.43 (3H, s, Me), 3.11 (1H, dd, J = 4.8, 17.5 Hz, 4-H_{trans}), 3.70 (1H, dd, J = 11.7, 17.5 Hz, 4-H_{cis}), 4.26 (2H, q, J = 6.8 Hz, $C\underline{H}_2CH_3$), 4.68 (2H, s, CH_2), 5.59 (1H, dd, J = 4.8, 11.7 Hz, 5-H), 6.94-7.69 (m, 9 arom. H); ^{13}C-NMR (δ, $CDCl_3$): 14.0, 21.8, 42.3, 59.8, 65.2, 114.8, 125.1, 125.5, 127.5, 128.2, 128.8, 141.8, 153.3, 159.4, 168.6; IR (cm^{-1}): 1655, 1599, 1537, 1444, 1410, 1321, 1257, 1206, 1062, 960, 862, 756, 700; Anal. Calcd. for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.64. Found: 68.93; H, 6.11; N, 7.56.

1-Acetyl-3-[4-(aminocarbonyl-methoxy)phenly]-5-phenyl-2-pyrazoline (**9**). Obtained as white plates in 62% yield, mp 163-164 °C; ^{1}H-NMR (δ, DMSO-d_6): 2.30 (3H, s, Me), 3.09 (1H, dd, J = 4.3, 17.9 Hz, 4-H_{trans}), 3.84 (1H, dd, J = 11.6, 17.9 Hz, 4-H_{cis}), 4.67 (2H, s, CH_2), 5.52 (1H, dd, J = 4.3, 11.6 Hz, 5-H), 7.02-7.73 (m, 9 arom H), 9.82 (2H, s, NH_2); ^{13}C-NMR (δ, DMSO-d_6): 20.3, 21.5, 59.2, 65.8, 114.9, 124.4, 125.3, 127.0, 128.1, 128.5, 142.4, 153.7, 159.2, 166.1, 167.9; IR (cm^{-1}): 3481, 3144, 1694, 1656, 1597, 1534, 1441, 1416, 1321, 1248, 1210, 964, 963, 760, 702; Anal. Calcd. for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.45. Found: C, 67.72; H, 5.63; N, 12.52.

1-Acetyl-3-[4-(phenylaminocarbonyl-methoxy)phenyl]-5-phenyl-2-pyrazoline (**10**). Prepared as pale yellow plates in 73%, mp 205-206 °C; ^{1}H-NMR (δ, $CDCl_3$): 2.46 (3H, s, Me), 3.08 (1H, dd, J = 7.4, 17.2 Hz, 4-H_{trans}), 3.78 (1H, dd, J = 12.2, 17.2 Hz, 4-H_{cis}), 4.61 (2H, s, CH_2), 5.21 (1H, dd, J = 7.4, 12.2 Hz, 5-H), 6.74-7.69 (m, 14 arom. H), 8.21 (1H, s, NH); ^{13}C-NMR (δ, $CDCl_3$): 21.9, 42.3, 59.9, 67.6, 115.0, 120.1, 125.0, 125.5, 125.9, 127.6, 128.5, 128.9, 129.1, 136.6, 141.8, 153.0, 158.4, 165.6, 168.7; IR (cm^{-1}): 1673, 1598, 1536, 1498, 1445, 1389, 1321, 1243, 1175, 1120, 1069, 872, 830, 748, 699; Anal. Calcd. for $C_{25}H_{23}N_3O_3$: C, 72.62; H, 5.61; N, 10.16. Found: C, 72.71; H, 5.67; N, 10.07.

1,5-Diphenyl-3-[4-(phenylaminocarbonyl-methoxy)phenyl]-2-pyrazoline (**11**). Obtained as pale yellow needles in 71% yield, mp 212-213 °C; ^{1}H-NMR (δ, $CDCl_3$): 3.09 (1H, dd, J = 7.3, 17.4 Hz, 4-H_{trans}), 3.81 (1H, dd, J = 12.0, 17.4 Hz, 4-H_{cis}), 4.62 (2H, s, CH_2), 5.24 (1H, dd, J = 7.3, 12.0 Hz, 5-H), 6.70-7.81 (m, 19 arom. H), 8.24 (1H, s, NH); ^{13}C-NMR (δ, $CDCl_3$): 43.4, 64.6, 67.6, 111.7, 112.5, 113.4, 114.9, 119.4, 124.8, 124.9, 125.5, 125.8, 127.6, 128.5, 128.7, 129.1, 130.0, 134.7, 136.8, 142.3, 144.5, 145.8, 157.1, 166.0; IR (cm^{-1}): 1678, 1598, 1536, 1498, 1445, 1321, 1243, 1175, 1120, 1069, 872, 830, 748, 699; Anal. Calcd. for $C_{29}H_{25}N_3O_2$: C, 77.83, H, 5.63; N, 9.38. Found: 77.74; H, 5.69; N, 9.46.

1,5-Diphenyl-3-[4-(2-ethyl-6-methylphenylamino-carbonyl-methoxy)phenyl]-2-pyrazol-ine (1**2**). Isolated as white plates in 89% yield, mp 195-196 °C; ^{1}H-NMR (δ, $CDCl_3$): 1.16 (3H, t, J = 7.4 Hz, $CH_2C\underline{H}_3$), 2.23 (3H, s, Me), 2.56 (2H, q, J = 7.4, $C\underline{H}_2CH_3$), 3.12 (1H, dd, J = 7.4, 17.2 Hz, 4-H_{trans}), 3.83 (1H, dd, J = 12.4, 17.2 Hz, 4-H_{cis}), 4.73 (2H, s, CH_2), 5.26 (1H, dd, J = 7.4, 12.4 Hz, 5-H), 6.77-7.74 (m, 17 arom. H), 7.83 (1H, s, NH); ^{13}C-NMR (δ, $CDCl_3$): 14.5, 18.5, 24.8, 67.6, 114.6, 114.8, 125.3, 126.5, 127.5, 128.4, 128.7, 128.9, 129.1, 130.4, 135.9, 139.8, 141.1, 144.6, 151.1, 157.1, 166.9; IR (cm^{-1}): 1668, 1597, 1498, 1391, 1245, 1177, 1125, 1069, 873, 832, 748, 700; Anal. Calcd. for $C_{32}H_{31}N_3O_3$: C, 78.50; H, 6.38; N, 8.58. Found: C, 78.60; H, 6.32; N, 8.48.

General procedure for the preparation of 1-(2-carboxyphenyl)-2-pyrazolines 24-30

A mixture of the appropriate chalcone (**13**,**16-18,20-22**, 10.0 mmoles), (2-carboxyphenyl)-hydrazine (30.0 mmoles) and acetic acid (60 mL) was refluxed for 5 h, then poured onto crushed ice. The oily precipitate was extracted with chloroform. This solution was washed with brine, dried with $CaCl_2$ and the solvent was evaporated under reduced pressure. The residue was crystallized from methanol to obtain 1-(2-carboxyphenyl)-2-pyrazolines **24-30** (Scheme 2).

1-(2-Carboxyphenyl)-3,5-diphenyl-2-pyrazoline (**24**). Prepared as white needles in 61% yield, mp 140-141 °C; ^{1}H-NMR (δ, $CDCl_3$): 3.12 (1H, dd, J = 7.1, 17.2 Hz, 4-H_{trans}), 3.81 (1H, dd, J = 12.3, 17.2 Hz, 4-H_{cis}), 5.27 (1H, dd, J = 7.1, 12.3 Hz, 5-H), 6.78-7.73 (m, 14 arom. H); ^{13}C-NMR (δ, $CDCl_3$): 43.5, 64.4, 113.4, 119.1, 125.7, 125.8, 127.5, 128.5, 128.9, 129.1, 132.7, 142.9, 144.9, 146.7; IR (cm^{-1}): 1597, 1503, 1455, 1394, 1325, 1267, 1125, 1070, 1030, 873, 759, 692; Anal. Calcd. for $C_{22}H_{18}N_2O_2$: C, 77.l7; H, 5.30; N, 8.18. Found: C, 77.08; H, 5.36; N, 8.11.

1-(2-Carboxyphenyl)-3-(4-fluorophenyl)-5-phenyl-2-pyrazoline (**25**). Obtained as pale yellow needles in 59% yield, mp 136-137 °C; ^{1}H-NMR (δ, $CDCl_3$): 3.07 (1H, dd, J = 7.3, 16.8 Hz, 4-H_{trans}), 3.80 (1H, dd, J = 12.3, 16.8 Hz, 4-H_{cis}), 5.22 (1H, dd, J = 7.3, 12.3 Hz, 5-H), 6.75-7.69 (m, 13 arom. H); ^{13}H-NMR (δ, $CDCl_3$): 43.6, 64.6, 113.3, 115.3, 115.8, 119.1, 125.3, 125.8, 126.7, 127.6, 128.5, 128.9, 129.1, 142.5, 144.8, 145.8; IR (cm^{-1}): 1598, 1500, 1390, 1326, 1228, 1130, 1070, 874, 835, 745, 699; Anal. Calcd. for $C_{22}H_{17}FN_2O_2$: C, 73.32; H, 4.76; N, 7.77. Found: 73.40; H, 4.81; N, 7.69.

1-(2-Carboxyphenyl)-3-(4-chlorophenyl)-5-phenyl-2-pyrazoline (**26**). Isolated as yellow plates in 65% yield, mp 128-129 °C; ^{1}H-NMR (δ, $CDCl_3$): 3.08 (1H, dd, J = 7.3, 16.8 Hz, 4-H_{trans}), 3.77 (1H, dd, J = 12.4, 16.8 Hz, 4-H_{cis}), 5.24 (1H, dd, J = 7.3, 12.4 Hz, 5-H), 6.78-7.62 (m, 13 arom. H); ^{13}C-NMR (δ, $CDCl_3$): 43.3, 64.6, 113.4, 119.3, 125.8, 126.8, 127.6, 128.5, 128.7, 128.9, 129.2, 129.9, 130.7, 131.3, 134.2, 142.3, 144.6, 145.5; IR (cm^{-1}): 1598, 1502, 1322, 1245, 1129, 1089, 1011, 869, 826, 745, 701, Anal. Calcd. for $C_{22}H_{17}Cl\ N_2O_2$: C, 70.12; H, 4.55; N, 7.43. Found: C, 70.04; H, 4.61; N, 7.49.

3-(4-Bromophenyl)-1-(2-carboxyphenyl)-5-phenyl-2-pyrazoline (**27**). Obtained as pale yellow plates in 61% yield, mp 151-152 °C; ^{1}H-NMR (δ, $CDCl_3$): 3.08 (1H, dd, J = 7.4, 17.1 Hz, 4-H_{trans}), 3.79 (1H, dd, J = 12.4, 17.1 Hz, 4-H_{cis}), 5.77 (1H, dd, J = 7.4, 12.4 Hz, 5-H), 6.79-7.78 (m, 13 arom. H); ^{13}C-NMR (δ, $CDCl_3$): 43.3, 64.6, 113.4, 119.3, 125.3, 125.8, 127.1, 127.4, 127.6, 128.5, 128.7, 128.9, 129.2, 131.6, 131.7, 142.3, 144.5, 145.5; IR (cm^{-1}): 1597, 1545, 1501, 1324, 1243, 1133, 1072, 1008, 871, 822, 744, 693; Anal. Calcd. for $C_{22}H_{17}BrN_2O_2$: C, 62.72; H, 4.07; N, 6.65. Found: C, 62.64; H, 4.11; N, 6.57.

1-(2-Carboxyphenyl)-5-(4-methylphenyl)-3-phenyl-2-pyrazoline (**28**). Prepared as white needles in 60% yield, mp 133-134 °C; ^{1}H-NMR (δ, $CDCl_3$): 2.60 (3H, s, Me), 3.08 (1H, dd, J = 7.4, 17.3 Hz, 4-H_{trans}), 3.76 (1H, dd, J = 11.9, 17.3 Hz, 4-H_{cis}), 5.21 (1H, dd, J = 7.4, 11.9 Hz, 5-H), 6.72-7.74 (m, 13 arom. H); ^{13}C-NMR (δ, $CDCl_3$): 21.0, 43.5, 64.2, 113.3, 118.9, 125.7, 125.8, 128.5, 128.8, 129.7, 132.8, 137.2, 139.6, 144.9, 146.7; IR (cm^{-1}): 1597, 1503, 1460, 1447, 1392, 1334, 1271, 1124, 1069, 1001, 869, 810, 756, 688; Anal. Calcd. for $C_{23}H_{20}N_2O_2$: C, 77.15; H, 5.65; N, 7.86. Found: C, 77.61; H, 5.69; N, 7.78.

1-(2-Carboxyphenyl)-5-(4-chlorophenyl)-3-phenyl-2-pyrazoline (**29**). Isolated as pale yellow plates in 58% yield, mp 131-132 °C; ^{1}H-NMR (δ, $CDCl_3$): 3.08 (1H, dd, J = 7.3, 17.2 Hz, 4-H_{trans}), 3.82 (1H, dd, J = 12.4, 17.2 Hz, 4-H_{cis}), 5.23 (1H, dd. J = 7.3, 12.4 Hz, 5-H), 6.80-7.74 (m, 13 arom. H); ^{13}C-NMR (δ, $CDCl_3$): 43.4, 63.8, 113.4, 119.3, 125.7, 128.5, 128.7, 128.9, 133.3, 141.0, 144.6, 146.7; IR (cm^{-1}): 1594, 1493, 1455, 1392, 1319, 1240, 1127, 1090, 1068,

1014, 869, 823, 754, 689; Anal. Calcd. for $C_{22}H_{17}ClN_2O_2$: C, 70.12; H, 4.55; N, 7.43. Found: C, 70.19; H, 4.50; N, 7.36.

5-(4-Bromophenyl)-1-(2-carboxyphenyl)-3-phenyl-2-pyrazoline (**30**). Prepared as yellow plates in 64% yield, mp 134-135 °C; ^{1}H-NMR (δ, $CDCl_3$): 3.09 (1H, dd, J = 7.3, 17.3 Hz, 4-H_{trans}), 3.81 (1H, dd, J = 12.8, 17.3 Hz, 4-H_{cis}), 5.23 (1H, dd, J = 7.3, 12.4 Hz, 5-H), 6.80-7.73 (m, 13 arom. H); ^{13}C-NMR (δ, $CDCl_3$): 43.3, 63.8, 113.3, 119.3, 121.3, 125.7, 127.6, 128.5, 128.7, 128.9, 132.3, 132.5, 141.6, 144.6, 146.7; IR (cm^{-1}): 1596, 1502, 1447, 1393, 1334, 1128, 1070, 1011, 869, 821, 753, 689; Anal. Calcd. for $C_{22}H_{17}BrN_2O_2$: C, 62.72; H, 4.07; N, 6.65. Found: C, 62.81; H, 4.01; N, 6.72.

General procedure for the synthesis of 1-(4-carboxyphenyl)-2-pyrazolines 31-41

A mixture of chalcone (**13-23**, 10.0 mmoles), (4-carboxyphenyl)hydrazine (30.0 mmoles) and acetic acid (50 mL) was heated at reflux for 7 h, then pured onto crushed ice. The precipitate was separated by filtration, washed with water and crystallized from methanol to afford 1-(4-carboxyphenyl)-2-pyrazolines **31-41** (Scheme 2).

1-(4-Carboxyphenyl)-3,5-diphenyl-2-pyrazoline (**31**). Isolated as white needles in 61% yield, mp 242-243 °C; ^{1}H-NMR (δ, DMSO-d_6): 3.20 (1H, dd, J = 5.2, 17.9 Hz, 4-H_{trans}), 3.89 (1H, dd, J = 12.1, 17.9 Hz, 4-H_{cis}), 5.63 (1H, dd, J = 5.2, 12.1 Hz, 5-H), 7.04-7.91 (m, 14 arom. H), 12.29 (1H, s, COOH); ^{13}C-NMR (δ, DMSO-d_6): 42.9, 62.3, 111.8, 119.8, 125.2, 125.9, 127.4, 128.6, 129.1, 130.7, 131.6, 141.7, 149.5, 167.1; IR (cm^{-1}): 1671, 1598, 1522, 1405, 1326, 1281, 1174, 1131, 1095, 868, 770, 696; Anal. Calcd. for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.27; H, 5.26; N, 8.26.

1-(4-Carboxyphenyl)-3-(4-methylphenyl)-5-phenyl-2-pyrazoline (**32**). Prepared as yellow needles in 72% yield, mp 258-259 °C; ^{1}H-NMR (δ, DMSO-d_6): 2.38 (3H, s, Me), 3.09 (1H, dd, J = 4.7, 17.4 Hz, 4-H_{trans}), 3.88 (1H, dd, J = 12.0, 17.4 Hz, 4-H_{cis}), 5.59 (1H, dd, J = 4.7, 12.0 Hz, 5-H), 7.01-7.78 (m, 13 arom. H), 12.24 (1H, s, COOH); ^{13}C-NMR (δ, DMSO-d_6): 20.8, 42.9, 62.2, 111.7, 119.6, 125.5, 125.9, 127.4, 128.9, 129.2, 130.7, 138.9, 141.7, 146.9, 149.6, 167.0; IR (cm^{-1}): 1672, 1599, 1512, 1395, 1282, 1174, 1127, 1094, 867, 843, 816, 771, 697; Anal. Calcd. for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.65; N, 7.86. Found: 77.43; H, 5.71; N, 7.92.

1-(4-Carboxyphenyl)-3-(4-methoxyphenyl)-5-phenyl-2-pyrazoline (**33**). Prepared as white needles in 57% yield, mp 265-266 °C; ^{1}H-NMR (δ, DMSO-d_6): 3.0.8 (1H, dd, J = 5.3, 17.9 Hz, 4-H_{trans}), 3.80 (3H, s, MeO), 3.97 (1H, dd, J = 11.9, 17.9 Hz, 4-H_{cis}), 5.60 (1H, dd, J = 5.3, 11.9 Hz, 5-H), 6.98-7.78 (m, 13 arom. H), 12.24 (1H, s, COOH); ^{13}C-NMR (δ, DMSO-d_6): 43.1, 52.5, 62.1, 111.6, 114.1, 119.4, 124.2, 125.5, 127.4, 127.6, 128.9, 130.7, 141.8, 147.0, 149.5, 160.1, 167.1; IR (cm^{-1}): 1671, 1598, 1511, 1393, 1280, 1252, 1170, 1127, 1094, 842, 770, 695; Anal. Calcd. for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52. Found: C, 74.26; H, 5.36; N, 7.59.

1-(4-Carboxyphenyl)-3-(4-fluorophenyl)-5-phenyl-2-pyrazoline (**34**). Obtained as pale yellow plates in 76% yield, mp 234-235 °C; ^{1}H-NMR (δ, DMSO-d_6): 3.18 (1H, dd, J = 5.2, 17.4 Hz, 4-H_{trans}), 3.97 (1H, dd, J = 12.1, 17.4 Hz, 4-H_{cis}), 5.62 (1H, dd, J = 5.2, 12.1 Hz, 5-H), 7.01-7.86

(m, 13 arom. H), 12.36 (1H, s, COOH); ^{13}C-NMR (δ, DMSO-d_6): 42.9, 62.3, 111.8, 115.3, 115.8, 119.8, 125.5, 127.4, 128.0, 128.3, 128.9, 130.6, 141.6, 146.8, 148.6, 166.9; IR (cm^{-1}): 1672, 1602, 1509, 1397, 1286, 1228, 1175, 1133, 1096, 872, 838, 770, 699; Anal. Calcd. for $C_{22}H_{17}FN_2O_2$: C, 73.32; H, 4.75; N, 7.77. Found: C, 73.41; H, 4.71; N, 7.85.

1-(4-Carboxyphenyl)-3-(3-chlorophenyl)-5-phenyl-2-pyrazoline (**35**). Isolated as yellow needles in 68% yield, mp 286-287 °C; ^{1}H-NMR (δ, DMSO-d_6): 3.19 (1H, dd, J = 5.1, 17.8 Hz, 4-H_{trans}), 3.97 (1H, dd, J = 12.0, 17.8 Hz, 4-H_{cis}), 5.64 (1H, dd, J = 5.1, 12.0 Hz, 5-H), 7.04-7.80 (m, 13 arom. H), 12.36 (1H, s, COOH); ^{13}C-NMR (δ, DMSO-d_6): 42.7, 62.5, 111.9, 120.1, 125.6, 127.6, 128.6, 128.9, 130.6, 130.7, 133.6, 141.6, 146.7, 148.5, 167.0; IR (cm^{-1}): 1667, 1600, 1517, 1410, 1387, 1280, 1174, 1127, 1089, 871, 844, 758, 698; Anal. Calcd. for $C_{22}H_{17}ClN_2O_2$: C, 70.12; H, 4.55; N, 7.43. Found: C, 70.04; H, 4.60; N, 7.36.

3-(4-Bromophenyl)-1-(4-carboxyphenyl)-5-phenyl-2-pyrazoline (**36**). Prepared as white plates in 61% yield, mp 293-294 °C; ^{1}H-NMR (δ, DMSO-d_6): 3.18 (1H, dd, J = 5.5, 18.0 Hz, 4-H_{trans}), 3.96 (1H, dd, J = 12.0, 18.0 Hz, 4-H_{cis}), 5.66 (1H, dd, J = 5.5, 12.0 Hz, 5-H), 7.06-7.78 (m, 13 arom. H), 12.36 (1H, s, COOH); ^{13}C-NMR (δ, DMSO-d_6): 42.6, 62.4, 111.9, 120.1, 122.2, 125.5, 127.5, 127.8, 128.9, 130.6, 131.5, 141.5, 146.6, 148.5, 166.9; IR (cm^{-1}): 1668, 1599, 1516, 1409, 1385, 1282, 1174, 1128, 1007, 770, 698; Anal. Calcd. for $C_{22}H_{17}BrN_2O_2$: C, 62.72; H, 4.07; N, 6.65. Found: C, 62.64; H, 4.03; N, 6.59.

1-(4-Carboxyphenyl)-3-(4-nitrophenyl)-5-phenyl-2-pyrazoline (**37**). Obtained as yellow plates in 68% yield, mp 277-278 °C; ^{1}H-NMR (δ, DMSO-d_6): 3.22 (1H, dd, J = 5.0, 18.1 Hz, 4-H_{trans}), 4.02 (1H, dd, J = 12.5, 18.1 Hz, 4-H_{cis}), 5.76 (1H, dd, J = 5.0, 12.5 Hz, 5-H), 7.14-8.29 (m, 13 arom. H), 12.42 (1H, s, COOH); ^{13}C-NMR (δ, DMSO-d_6): 42.4, 62.9, 112.5, 120.9, 123.8, 125.6, 126.7, 127.6, 129.0, 130.7, 138.0, 141.3, 146.1, 146.9, 147.5, 166.9; IR (cm^{-1}): 1686, 1595, 1552, 1514, 1430, 1339, 1277, 1236, 1174, 1135, 1105, 848, 770, 6.99; Anal. Calcd. for $C_{22}H_{17}N_3O_4$: C, 68.21; H, 4.42; N, 10.84. Found: C, 68.30; H, 4.38; N, 10.92.

1-(4-Carboxyphenyl)-5-(4-methylphenyl)-3-phenyl-2-pyrazoline (**38**). Isolated as white needles in 84%, mp 241-242 °C; ^{1}H-NMR (δ, DMSO-d_6): 2.22 (3H, s, Me), 3.18 (1H, dd, J = 5.1, 17.4 Hz, 4-H_{trans}), 3.98 (1H, dd, J = 11.8, 17.4 Hz, 4-H_{cis}), 5.60 (1H, dd, J = 5.1, 11.8 Hz, 5-H), 7.04-7.82 (m, 13 arom. H), 12.10 (1H, s, COOH); ^{13}C-NMR (δ, DMSO-d_6): 20.5, 42.9, 62.1, 111.9, 119.8, 125.5, 125.9, 128.6, 129.5, 130.6, 131.7, 136.6, 138.7, 146.9, 167.1; IR (cm^{-1}): 1667, 1595, 1522, 1410, 1289, 1175, 1136, 873, 842, 773, 691; Anal. Calcd. for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.65; N, 7.85 . Found: C, 77.43; H, 5.60; N, 7.92.

1-(4-Carboxyphenyl)-5-(4-chlorophenyl)-3-phenyl-2-pyrazoline (**39**). Prepared as pale yellow plates in 81% yield, mp 226-227 °C; ^{1}H-NMR (δ, DMSO-d_6): 3.20 (1H, dd, J = 4.9, 17.7 Hz, 4-H_{trans}), 3.98 (1H, dd, J = 12.1, 17.7 Hz, 4-H_{cis}), 5.67 (1H, dd, J = 4.9, 12.1 Hz, 5-H), 7.08-7.80 (m, 13 arom. H), 12.30 (1H, s, COOH); ^{13}C-NMR (δ, DMSO-d_6): 42.6, 61.6, 111.9, 120.0, 125.9, 127.6, 128.6, 128.9, 129.2, 130.7, 131.6, 132.0, 140.6, 146.7, 149.6, 168.4; IR (cm^{-1}): 1677, 1600, 1519, 1491, 1401, 1311, 1288, 1176, 1128, 1092, 1014, 824, 770, 691; Anal. Calcd. for $C_{22}H_{17}ClN_2O_2$: C, 70.12; H, 4.55; N, 7.43. Found: C, 70.20, H, 4.51; N, 7.51.

5-(4-Bromophenyl)-1-(4-carboxyphenyl)-3-phenyl-2-pyrazoline (**40**). Obtained as yellow needles in 62% yield, mp 214-215 °C; ^{1}H-NMR (δ, DMSO-d_6): 3.20 (1H, dd, J = 5.2, 18.1 Hz, 4-H_{trans}), 4.01 (1H, dd, J = 11.9, 18.1 Hz, 4-H_{cis}), 5.68 (1H, dd, J = 5.2, 11.9 Hz, 5-H), 7.02-7.83 (m, 13 arom. H), 12.38 (1H, s, COOH); ^{13}C-NMR (δ, DMSO-d_6): 42.6, 61.6, 111.8, 119.9, 120.5, 125.9, 127.9, 128.6, 129.2, 130.7, 131.5, 131.8, 141.0, 146.6, 149.6, 167.0; IR (cm^{-1}): 1676, 1600, 1520, 1487, 1403, 1287, 1175, 1130, 1095, 1011, 873, 821, 770, 691; Anal. Calcd. for $C_{22}H_{17}BrN_2O_2$: C, 62.72; H, 4.07; N, 6.65. Found: 62.79; H, 4.11; N, 6.72.

1-(4-Carboxyphenyl)-5-(4-nitrophenyl)-3-phenyl-2-pyrazoline (**41**). Isolated as yellow plates in 77% yield, mp 269-270 °C; ^{1}H-NMR (δ, DMSO-d_6): 3.22 (1H, dd, J = 5.2, 17.9 Hz, 4-H_{trans}), 4.04 (1H, dd, J = 12.5, 17.9 Hz, 4-H_{cis}), 5.82 (1H, dd, J = 5.2, 12.5 Hz, 5-H), 7.04-8.21 (m, 13 arom. H), 12.30 (1H, s, COOH); ^{13}C-NMR (δ, DMSO-d_6): 42.5, 61.6, 111.6, 112.8, 123.7, 124.1, 126.0, 127.1, 128.2, 128.6, 129.3, 130.7, 146.8, 149.1, 149.7, 166.9; IR (cm^{-1}): 1672, 1598, 1520, 1400, 1342, 1287, 1257, 1171, 1108, 847, 770, 692; Anal. Calcd. for $C_{22}H_{17}N_3O_4$: C, 68.21; H, 4.42; N, 10.84. Found: C, 68.16; H, 4.47; N, 10.75.

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