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Synthesis of new derivatives of 1-(3-aminophenyl)-4-benzoyl-5-phenyl-1*H*-pyrazole-3-carboxylic acid

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Abstract: 1-(3-Aminophenyl)-4-benzoyl-5-phenyl-1*H*-pyrazole-3-carboxylic acid (**1**) was synthesized according to the literature.¹ 2-(3-Aminophenyl)-2,6-dihydro-3,4-diphenyl-7*H*-pyrazolo[3,4-*d*]pyridazin-7-one (**5**) was obtained by the cyclocondensation reaction of **1** with hydrazine hydrate. New pyrazole derivatives of compounds **1** and **5** were synthesized by their reaction with β -diketones, β -ketoesters, β -naphthol, phenol and various other reagents. The structures of the synthesized compounds were characterized by ¹H-NMR, ¹³C-NMR, IR and mass spectroscopy, as well as elemental analysis.

Keywords: pyrazole-3-carboxylic acid; pyridazin; diazonium salts; cyclocondensation.

INTRODUCTION

It is known that pyrazole derivatives having heteroaryl groups attached as substituents exhibit significant biological activity and that some pyrazolo-pyridazine compounds containing heteroaryl groups are used to treat many diseases.^{2–4} On the other hand, diazonium salts have been the focus of great interest for a long time since they play a crucial role in organic syntheses and are commercially important coloring agents.^{5,6}

Arene diazonium groups not only couple to activated aromatic carbon atoms, but may also undergo coupling reactions with aliphatic compounds containing active methylene groups. The facilitated abstraction of the acidic proton in β -diketones and β -ketoesters leads to the formation of a resonance stable anion, which can, therefore, behave as a good nucleophile. Thus, the coupling of this anion with aryl diazonium chlorides gives 2-aryloxy-hydrazo derivatives, from which azo-hydrazo substituted heterocyclic compounds can be obtained. These

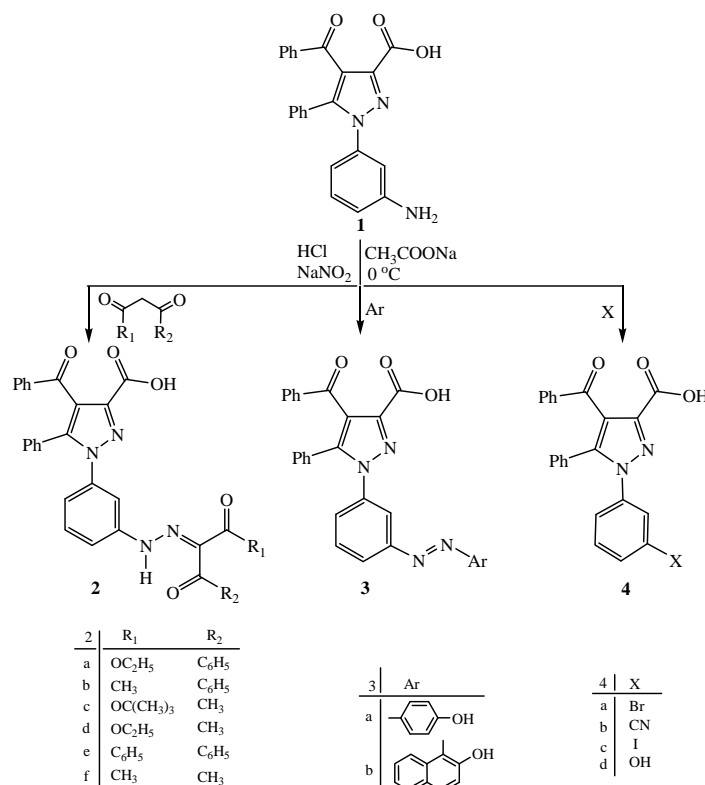
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compounds play a significant role in the dye industry and, in addition, enable the synthesis of heterocyclic compounds with different biological activities. Hence, these coupling products are among the most investigated groups of compounds.^{2,7-9}

Commencing from these facts, an attempt was made to expand the research on the preparation of different derivatives of pyrazole carboxylic acid compounds, which are biologically very important and exhibit pharmaceutical activities.^{2,5,7}

RESULTS AND DISCUSSION

In this study, first the diazonium salts from compounds **1** and **5**, which contain aromatic primary amine groups, were prepared *in situ* (Schemes 1 and 2).^{2,5,6} For this purpose, compounds **1** and **5** were dissolved in an ethanol–water mixture (50 %) containing sodium acetate and the temperature was kept constant (0–5 °C). Three moles of acid were used per mole of the amine compound in the diazotization reaction.^{10,11} In the experiments, different pH ranges were tested and the best yield was observed in the pH range 3.5–4.0.



Scheme 1. The synthesis of compounds **2a–f**, **3a–b** and **4a–d**.

In this study, as a result of the coupling reactions of **1** with various β -dicarbonyl compounds that contained an active aliphatic C–H group, derivatives **2a–f** were synthesized in 42–86 % yield. In all these compounds, due to the unpaired electron pairs on the nitrogen atoms, the proton that transferred to the base was subject to resonance. Thus, the products formed may be in the form of azo ($-\text{N}=\text{N}-$) or hydrazo ($-\text{NH}-\text{N}=\text{C}$) tautomeric structures.^{12–17} However, in the present study, an examination of the ^1H -NMR and IR spectra clearly revealed that the signals belonging to compounds **2a–d** at δ 11.90–11.20 ppm and in the range of 3475–3414 cm^{-1} stem from the hydrogen on the nitrogen in the corresponding hydrazo forms ($-\text{NH}-\text{N}=\text{C}$) (Fig. 1).

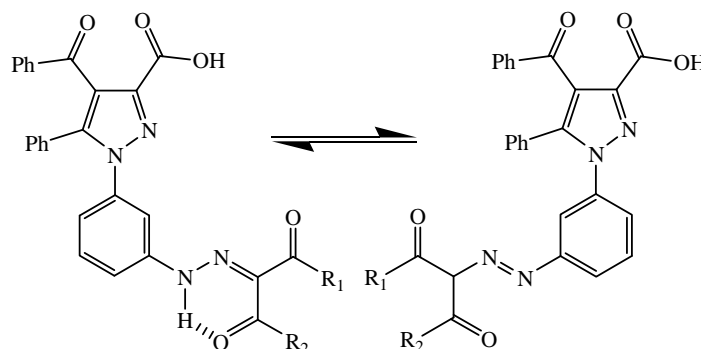
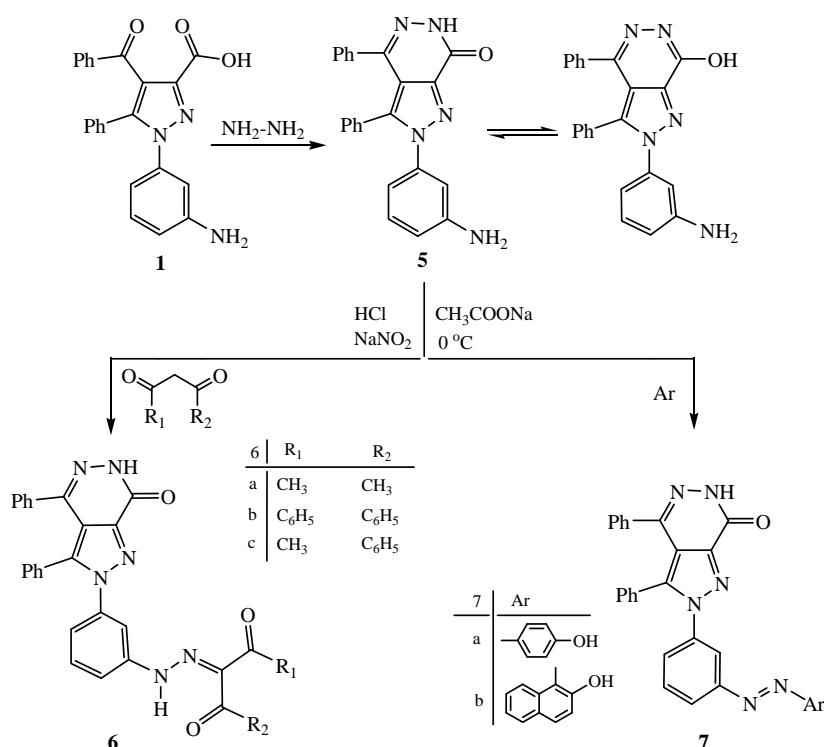


Fig. 1. Possible tautomeric structures for compounds **2a–f**.

On reaction of compound **1** with phenol and β -naphthol, derivatives **3a** (74 % yield) and **3b** (45% yield) were obtained, respectively. The structures of the compounds were verified by their spectral data (see EXPERIMENTAL). An examination of their resonance structures revealed that although the aryl diazonium ion, bearing partial positive charges on both nitrogen atoms, exhibits weak electrophilic character, it normally formed azo compounds in the diazo coupling reaction with the quite active aromatic compounds phenol and β -naphthol, giving the corresponding diazo compounds **3a** and **3b**. The mechanism of coupling reactions is the same as those of electrophilic aromatic replacement reactions. In the first step, the electrophile binds to the carbon of the nucleophilic substrate through a covalent bond and an intermediate product is formed. Subsequently, a proton transfer to the base occurs. In the phenol and β -naphthol derivatives, coupling occurs almost exclusively in the para position if the para position is free. If the para position is occupied, then coupling occurs in the ortho position.^{18,19}

In the syntheses, the Sandmeyer reaction²⁰ was employed, in which Cu(I) salts as catalysts together with the potassium salts of Br^- and CN^- were used to obtain derivatives **4a** and **b** in 46 and 88 % yield, respectively.²⁰ For replacement

by I^- , having a strong nucleophilic character, the KI alone was sufficient without any necessity for a catalyst and thus, compound **4c** was obtained. On heating the diazo compound with H_2O to 100°C , derivative **4d** was obtained in high yield (85 %). In addition, the cyclocondensation of compound **1** with anhydrous hydrazine hydrate yielded a pyrazolo[3,4-*d*]pyridazin-7-one (**5**).^{1,21} During the reaction of intermediary **5** with different β -diketones, compounds **6a–c** were obtained. Derivatives **7a** and **7b** were synthesized by the coupling reactions of **5** with phenol and β -naphthol, respectively (Scheme 2).



Scheme 2. The synthesis of compounds **6a–c** and **7a–b**.

The yields, melting points, analytic data and spectral data of the prepared compounds are given below.

4-Benzoyl-1-(3-(2-(1-benzoyl-2-ethoxy-2-oxoethylidene)hydrazinyl)phenyl)-5-phenyl-1H-pyrazole-3-carboxylic acid (2a). Yield: 42 %; m.p. $147\text{--}148^\circ\text{C}$. Anal. Calcd. for $\text{C}_{34}\text{H}_{26}\text{N}_4\text{O}_6$: C, 69.62; H, 4.47; N, 9.55 %. Found: C, 69.45; H, 4.58; N, 9.50 %. IR (KBr, cm^{-1}): 2500–3500 (COOH), 3060 (Ar CH), 2901 and 2835 (aliphatic CH), 1724 and 1666 (C=O), 1607–1463 (Ar C=C and C=N). ^1H -NMR (400 MHz, $\text{DMSO}-d_6$, δ / ppm): 12.70 (1H, *br s*, COOH), 11.90 (1H, *br s*, NH=N=C), 7.20–7.90 (19H, *m*, ArH), 4.30 (2H, *q*, $J = 7.1$ Hz, OCH_2), 1.30

(3H, *t*, $J = 7.0$ Hz, CH₃). ¹³C-NMR (100 MHz, DMSO-*d*₆, δ / ppm): 191.65 and 189.27 (benzoyl C=O), 163.46 (ester C=O), 162.75 (acid C=O), 145.60 (NH-N=C), 142.85 (pyrazole C-3), 61.79 (OCH₂), 14.33 (CH₃), 140.13, 138.34, 137.20, 133.67, 133.08, 130.38, 130.04, 129.83, 129.70, 129.65, 129.57, 129.53, 129.01, 128.96, 128.73, 128.61, 128.36, 128.25, 123.31, 120.35.

4-Benzoyl-1-(3-(2-(1-benzoyl-2-oxopropylidene)hydrazinyl)phenyl)-5-phenyl-1H-pyrazole-3-carboxylic acid (2b). Yield: 86 %; m.p. 126–128 °C. Anal. Calcd. for C₃₃H₂₄N₄O₅: C, 71.21; H, 4.35; N, 10.07 %. Found: C, 69.32; H, 4.65; N, 9.57 %. IR (KBr, cm⁻¹): 2600–3500 (COOH), 3061 (Ar CH), 2950 (aliphatic CH), 1680 and 1665 (C=O), 1601–1461 (Ar C=C and C=N). ¹H-NMR (400 MHz, DMSO-*d*₆, δ / ppm): 13.09 (1H, *br s*, COOH), 11.23 (1H, *br s*, NH-N=C), 6.90–7.90 (19H, *m*, ArH), 2.50 (3H, *s*, CH₃). ¹³C-NMR (100 MHz, DMSO-*d*₆, δ / ppm): 196.49 (acetyl C=O), 195.43 and 191.30 (benzoyl C=O), 162.78 (acid C=O), 144.32 (NH-N=C), 143.09 (pyrazole C-3), 25.40 (CH₃), 140.13, 139.97, 138.09, 135.93, 133.93, 130.63, 130.02, 129.81, 129.53, 129.33, 129.21, 129.14, 129.04, 128.98, 128.91, 128.40, 128.28, 127.41, 123.50, 112.19; MS (CI) (*m/z*): 557.0 (M+1).

4-Benzoyl-1-(3-(2-(1-(tert-butoxycarbonyl)-2-oxopropylidene)hydrazinyl)phenyl)-5-phenyl-1H-pyrazole-3-carboxylic acid (2c). Yield: 49 %; m.p. 230–231 °C. Anal. Calcd. for C₃₁H₂₈N₄O₆: C, 67.38; H, 5.11; N, 10.14 %. Found: C, 67.25; H, 5.15; N, 10.17 %. IR (KBr, cm⁻¹): 2500–3500 (COOH), 3415 (NH), 3059 (Ar CH), 2900 and 2835 (aliphatic CH), 1718 and 1666 (C=O), 1605–1461 (Ar C=C and C=N). ¹H-NMR (400 MHz, DMSO-*d*₆, δ / ppm): 12.70 (1H, *br s*, COOH), 11.20 (1H, *br s*, NH-N=C), 6.90–7.90 (14H, *m*, ArH), 2.60 (9H, *s*, OC(CH₃)₃), 1.50 (3H, *s*, CH₃). ¹³C-NMR (100 MHz, DMSO-*d*₆, δ / ppm): 195.47 (acetyl C=O), 191.86 (benzoyl C=O), 185.38 (acid C=O), 163.86 (ester C=O), 146.96 (NH-N=C), 145.31 (pyrazole C-3), 82.63 (OC(CH₃)₃), 28.39 (C(CH₃)₃), 21.58 (CH₃), 142.54, 140.18, 138.49, 135.70, 133.52, 130.60, 130.32, 129.97, 129.48, 129.20, 128.95, 128.77, 127.50, 123.19, 121.95, 115.12.

4-Benzoyl-1-(3-(2-(1-(ethoxycarbonyl)-2-oxopropylidene)hydrazinyl)phenyl)-5-phenyl-1H-pyrazole-3-carboxylic acid (2d). Yield: 47 %; m.p. 240–242 °C. Anal. Calcd. for C₂₉H₂₄N₄O₆: C, 66.41; H, 4.61; N, 10.68 %. Found: C, 66.29; H, 4.65; N, 10.65 %. IR (KBr, cm⁻¹): 2600–3500 (COOH), 3415 (NH), 3060 (Ar CH), 2883 (aliphatic CH), 1665 (C=O), 1609–1460 (Ar C=C and C=N). ¹H-NMR (400 MHz, DMSO-*d*₆, δ / ppm): 12.80 (1H, *br s*, COOH), 11.60 (1H, *br s*, NH-N=C), 7.80–7.10 (14H, *m*, ArH), 4.30 (2H, *q*, $J = 7.1$ Hz, OCH₂), 2.26 (3H, *s*, CH₃), 1.26 (3H, *t*, $J = 7.1$ Hz, OCH₂CH₃). ¹³C-NMR (100 MHz, DMSO-*d*₆, δ / ppm): 195.47 (acetyl C=O), 191.86 (benzoyl C=O), 185.38 (acid C=O), 163.86 (ester C=O), 145.90 (NH-N=C), 144.21 (pyrazole C-3), 60.93 (OCH₂), 24.40 (O=CCH₃), 14.20 (CH₂CH₃), 142.35, 139.15, 138.45, 135.50, 134.01, 130.65, 130.40, 130.12, 129.45, 129.32, 128.85, 128.53, 127.60, 123.29, 112.10.

4-Benzoyl-1-(3-(2-(1-benzoyl-2-oxo-2-phenylethylidene)hydrazinyl)phenyl)-5-phenyl-1H-pyrazole-3-carboxylic acid (2e). Yield: 55 %; m.p. 205–206 °C. Anal. Calcd. for C₃₈H₂₆N₄O₅: C, 73.78; H, 4.24; N, 9.06 %. Found: C, 73.67; H, 4.30; N, 9.11 %. IR (KBr, cm⁻¹): 2500–3500 (COOH), 3422 (NH), 3059 (Ar CH), 1725 and 1664 (C=O), 1599–1460 (Ar C=C and C=N). ¹H-NMR (400 MHz, DMSO-*d*₆, δ / ppm): 13.70 (1H, *br s*, COOH), 13.20 (1H, *br s*, NH–N=C), 7.75–7.15 (24H, *m*, ArH). ¹³C-NMR (100 MHz, DMSO-*d*₆, δ / ppm): 197.46, 196.79 and 191.28 (benzoyl C=O), 162.78 (acid C=O), 143.43 (NH–N=C), 143.21 (pyrazole C–3), 113.60 (pyrazole C–4), 143.12, 142.99, 140.13, 139.96, 138.09, 134.53, 133.94, 130.71, 130.49, 130.11, 130.04, 129.82, 129.57, 129.13, 129.03, 128.97, 128.45, 128.27, 128.18, 123.48, 122.38, 118.30, 116.96.

1-(3-(2-(1-Acetyl-2-oxo-propylidene)hydrazinyl)phenyl)-4-benzoyl-5-phenyl-1H-pyrazole-3-carboxylic acid (2f). Yield: 55 %; m.p. 222–224 °C. Anal. Calcd. for C₂₈H₂₂N₄O₅: C, 68.01; H, 4.48; N, 11.33 %. Found: C, 67.89; H, 4.53; N, 11.35 %. IR (KBr, cm⁻¹): 2500–3500 (COOH), 3422 (NH), 3059 (Ar CH), 1725 and 1664 (C=O), 1599–1460 (Ar C=C and C=N); ¹H-NMR (400 MHz, DMSO-*d*₆, δ / ppm): 13.75 (1H, *br s*, COOH), 13.15 (1H, *br s*, NH–N=C), 7.80–7.20 (14H, *m*, ArH), 2.45 and 2.29 (6H, *s*, 2CH₃). ¹³C-NMR (100 MHz, DMSO-*d*₆, δ / ppm): 197.49 and 196.78 (acetyl C=O), 191.25 (benzoyl C=O), 162.70 (acid C=O), 143.43 (NH–N=C), 143.19 (pyrazole C–3), 113.57 (pyrazole C–4), 31.67 and 26.88 (CH₃), 142.99, 140.11, 138.06, 134.59, 133.94, 130.72, 130.02, 129.81, 129.54, 129.13, 129.02, 128.16, 123.48, 122.36, 116.96. MS (CI) (*m/z*): 495.0 (M+1).

4-Benzoyl-1-(3-((4-hydroxyphenyl)diazenyl)phenyl)-5-phenyl-1H-pyrazole-3-carboxylic acid (3a). Yield: 74 %; m.p. 286–288 °C. Anal. Calcd. for C₂₉H₂₀N₄O₄: C, 71.30; H, 4.13; N, 11.47 %. Found: C, 71.17; H, 4.18; N, 11.45 %. IR (KBr, cm⁻¹): 2700–3600 (COOH), 3416 (NH), 3060 (Ar CH), 1663 (C=O), 1607–1494 (Ar C=C and C=N), 1354 (ArOH); ¹H-NMR (400 MHz, DMSO-*d*₆, δ / ppm): 12.95 (1H, *br s*, COOH), 7.85–7.15 (18H, *m*, ArH), 6.95 (1H, *d*, *J* = 8.7 Hz, ArOH). ¹³C-NMR (100 MHz, DMSO-*d*₆, δ / ppm): 192.38 (benzoyl C=O), 164.92 (acid C=O), 150.13 (C=C–OH), 149.50 (ArC–N=N), 145.15 (pyrazole C–3), 96.37 (pyrazole C–4), 143.25, 141.87, 140.34, 138.82, 135.40, 133.24, 130.75, 130.41, 130.15, 129.86, 129.44, 129.18, 128.97, 128.82, 128.40, 122.99, 116.74.

4-Benzoyl-1-(3-((2-hydroxynaphthalen-1-yl)diazenyl)phenyl)-5-phenyl-1H-pyrazole-3-carboxylic acid (3b). Yield: 45 %; m.p. 261–263 °C. Anal. Calcd. for C₃₃H₂₂N₄O₄: C, 73.60; H, 4.12; N, 10.40 %. Found: C, 73.48; H, 4.19; N, 10.47 %. IR (KBr, cm⁻¹): 2500–3600 (COOH), 3415 (NH), 3064 (Ar CH), 1665 (C=O), 1609–1493 (Ar C=C and C=N), 1354 (ArOH). ¹H-NMR (400 MHz, DMSO-*d*₆, δ / ppm): 15.54 (1H, *s*, ArOH), 13.30 (1H, *br s*, COOH), 8.26–6.86 (20H, *m*, ArH). ¹³C-NMR (100 MHz, DMSO-*d*₆, δ / ppm): 191.27 (benzoyl C=O), 171.37

(acid C=O), 162.77 (ArC–OH), 145.47 (pyrazole C–3), 143.47, 143.37, 141.33, 140.28, 138.12, 133.96, 132.93, 130.87, 130.15, 129.92, 129.90, 129.62, 129.35, 129.33, 129.14, 129.05, 128.31, 128.29, 126.67, 124.63, 124.50, 123.64, 121.99, 119.83, 114.90. MS (CI) (m/z): 539.0 (M+1).

4-Benzoyl-1-(3-bromophenyl)-5-phenyl-1H-pyrazole-3-carboxylic acid (4a). Yield: 46 %; m.p. 273–274 °C. Anal. Calcd. for $C_{23}H_{15}BrN_2O_3$: C, 61.76; H, 3.38; N, 6.26 %. Found: C, 61.55; H, 3.45; N, 6.22 %. IR (KBr, cm^{-1}): 2500–3500 (COOH), 3062 (Ar CH), 1666 (C=O), 1611–1448 (Ar C=C and C=N). 1H -NMR (400 MHz, DMSO- d_6 , δ / ppm): 13.20 (1H, *br s*, COOH), 7.82–7.21 (14H, *m*, ArH). ^{13}C -NMR (100 MHz, DMSO- d_6 , δ / ppm): 190.52 (benzoyl C=O), 165.28 (acid C=O), 144.47 (pyrazole C–3), 142.55, 141.30, 139.67, 138.25, 137.64, 134.06, 130.85, 130.26, 129.60, 129.30, 129.25, 129.08, 126.27, 123.75, 123.40, 122.50.

4-Benzoyl-1-(3-cyanophenyl)-5-phenyl-1H-pyrazole-3-carboxylic acid (4b). Yield: 88 %; m.p. 255–256 °C. Anal. Calcd. for $C_{24}H_{15}N_3O_3$: C, 73.27; H, 3.84; N, 10.68 %. Found: C, 73.15; H, 3.87; N, 10.74 %. IR (KBr, cm^{-1}): 2800–3600 (COOH), 3061 (Ar CH), 2130 (CN), 1661 (C=O), 1601–1426 (Ar C=C and C=N). 1H -NMR (400 MHz, DMSO- d_6 , δ / ppm): 13.80 (1H, *br s*, COOH), 7.95–6.70 (14H, *m*, ArH). ^{13}C -NMR (100 MHz, DMSO- d_6 , δ / ppm): 190.52, (benzoyl C=O), 165.35, (acid C=O), 144.48 (pyrazole C–3), 116.13 (CN), 143.25, 141.12, 139.68, 138.82, 137.63, 134.06, 130.53, 130.27, 129.62, 129.30, 129.08, 128.97, 127.88, 126.26, 123.07, 122.92.

4-Benzoyl-1-(3-iodophenyl)-5-phenyl-1H-pyrazole-3-carboxylic acid (4c). Yield: 70 %; m.p. 265–266 °C. Anal. Calcd. for $C_{23}H_{15}IN_2O_3$: C, 55.89; H, 3.06; N, 5.67 %. Found: C, 55.78; H, 3.11; N, 5.64 %. IR (KBr, cm^{-1}): 2500–3500 (COOH), 3059 (Ar CH), 1664 (C=O), 1608–1427 (Ar C=C and C=N). 1H -NMR (400 MHz, DMSO- d_6 , δ / ppm): 13.10 (1H, *br s*, COOH), 7.80–7.17 (14H, *m*, ArH). ^{13}C -NMR (100 MHz, DMSO- d_6 , δ / ppm): 191.28 (benzoyl C=O), 162.79 (acid C=O), 143.38 (pyrazole C–3), 95.20 (ArC–I), 139.96, 138.09, 133.92, 130.49, 130.10, 129.80, 129.56, 129.12, 128.97, 128.28, 127.10, 124.95, 123.44, 118.66, 107.62. MS (CI) (m/z): 495.0 (M+1).

4-Benzoyl-1-(3-hydroxyphenyl)-5-phenyl-1H-pyrazole-3-carboxylic acid (4d). Yield: 85 %; m.p. 235–237 °C. Anal. Calcd. for $C_{23}H_{16}N_2O_4$: C, 71.87; H, 4.20; N, 7.29 %. Found: C, 71.79; H, 4.26; N, 7.32 %. IR (KBr, cm^{-1}): 2700–3600 (COOH), 3059 (Ar CH), 1665 (C=O), 1607–1428 (Ar C=C and C=N). 1H -NMR (400 MHz, DMSO- d_6 , δ / ppm): 12.70 (1H, *br s*, COOH), 10.15 (1H, *br s*, Ar–OH), 7.74–7.15 (14H, *m*, ArH). ^{13}C -NMR (100 MHz, DMSO- d_6 , δ / ppm): 190.52 (benzoyl C=O), 165.30 (acid C=O), 152.13 (ArC–OH), 144.48 (pyrazole C–3), 143.22, 139.70, 137.61, 134.07, 130.55, 130.26, 129.89, 129.77, 129.62, 129.08, 128.91, 127.89, 127.41, 123.08, 114.96.

2-(3-(2-(1-Acetyl-2-oxopropylidene)hydrazinyl)phenyl)-2,6-dihydro-3,4-diphenyl-7H-pyrazolo[3,4-d]pyridazin-7-one (**6a**). Yield: 79 %; m.p. 214–216 °C. Anal. Calcd. for $C_{28}H_{22}N_6O_3$: C, 68.56; H, 4.52; N, 17.13 %. Found: C, 68.39; H, 4.54; N, 17.13 %. IR (KBr, cm^{-1}): 3456 and 3155 (NH), 3021 (Ar-CH), 2969 (aliphatic CH), 1740 (acetyl C=O), 1663 (amide C=O), 1608–1476 (Ar C=C and C=N). 1H -NMR (400 MHz, DMSO- d_6 , δ / ppm): 7.31 (1H, *br s*, NH), 7.56–6.92 (14H, *m*, ArH), 2.41 and 2.26 (6H, *s*, 2CH₃). ^{13}C -NMR (100 MHz, DMSO- d_6 , δ / ppm): 197.67 and 196.95 (tautomeric acetyl C=O), 156.79 (amide C=O), 144.28 (ArC–NH–N), 143.16 (pyrazole C–3), 140.58 (pyrazole C–5), 31.82 and 27.07 (tautomeric CH₃), 134.92, 131.20, 131.17, 129.66, 129.61, 128.96, 128.81, 128.77, 128.52, 128.47, 128.41, 128.38, 128.01, 123.17, 117.37, 117.35, 114.30.

2-(3-(2-(1-Benzoyl-2-oxo-2-phenylethylidene)hydrazinyl)phenyl)-2,6-dihydro-3,4-diphenyl-7H-pyrazolo[3,4-d]pyridazin-7-one (**6b**). Yield: 88 %; m.p. 234–236 °C. Anal. Calcd. for $C_{38}H_{26}N_6O_3$: C, 74.25; H, 4.26; N, 13.67 %. Found: C, 74.12; H, 4.28; N, 13.65 %. IR (KBr, cm^{-1}): 3461 and 3156 (NH), 3023 (Ar CH), 1740 (benzoyl C=O), 1670 (amide C=O), 1601–1475 (Ar C=C and C=N). 1H -NMR (400 MHz, DMSO- d_6 , δ / ppm): 11.60 (1H, *br s*, NH), 8.15–6.82 (24H, *m*, ArH). ^{13}C -NMR (100 MHz, DMSO- d_6 , δ / ppm): 186.02 (benzoyl C=O), 156.81 (amide C=O), 144.47 (ArC–NH–N), 144.27 (NH–N=C), 142.78 (pyrazole C–3), 140.88 (pyrazole C–5), 140.32, 135.29, 134.92, 133.69, 133.15, 131.15, 130.76, 130.61, 129.73, 129.61, 129.52, 129.29, 129.17, 128.94, 128.89, 128.79, 128.47, 128.40, 128.31, 128.09, 128.01, 117.37, 93.97.

2-(3-(2-(1-Benzoyl-2-oxopropylidene)hydrazinyl)phenyl)-2,6-dihydro-3,4-diphenyl-7H-pyrazolo[3,4-d]pyridazin-7-one (**6c**). Yield: 50 %; m.p. 256–257 °C. Anal. Calcd. for $C_{33}H_{24}N_6O_3$: C, 71.73; H, 4.38; N, 15.21 %. Found: C, 71.58; H, 4.41; N, 15.22 %. IR (KBr, cm^{-1}): 3393–3241 (NH), 3067 and 3028 (Ar CH), 1666 (C=O), 1608–1477 (Ar C=C and C=N). 1H -NMR (400 MHz, DMSO- d_6 , δ / ppm): 12.61 (1H, *br s*, NH), 7.45–6.92 (19H, *m*, ArH), 2.47 (3H, *s*, CH₃). ^{13}C -NMR (100 MHz, DMSO- d_6 , δ / ppm): 199.50 (acetyl C=O), 188.25 (benzoyl C=O), 156.81 (amide C=O), 144.28 (ArC–NH–N), 142.78 (pyrazole C–3), 140.89 (pyrazole C–5), 20.24 (CH₃), 140.33, 134.92, 131.33, 131.17, 130.77, 130.61, 129.61, 129.43, 129.09, 128.94, 128.78, 128.54, 128.47, 128.41, 128.01, 127.60, 123.86, 122.57, 117.37, 95.27.

2,6-Dihydro-2-(3-((4-hydroxyphenyl)diazinyl)phenyl)-3,4-diphenyl-7H-pyrazolo[3,4-d]pyridazin-7-one (**7a**). Yield: 68 %; m.p. 278–279 °C. Anal. Calcd. for $C_{29}H_{20}N_6O_2$: C, 71.89; H, 4.16; N, 17.35 %. Found: C, 71.78; H, 4.16; N, 17.37 %. IR (KBr, cm^{-1}): 3622 (OH), 3446–3160 (NH), 3062 and 3024 (Ar CH), 1662 (amide C=O), 1608–1476 (Ar C=C and C=N). 1H -NMR (400 MHz, DMSO- d_6 , δ / ppm): 12.54 (1H, *br s*, NH), 10.31 (1H, *s*, OH), 7.84–6.91 (18H, *m*, ArH). ^{13}C -NMR (100 MHz, DMSO- d_6 , δ / ppm): 162.28 (ArC–OH), 156.82 (amide C=O), 153.00 and 145.70, (ArC–N=N), 144.29, 142.90, 141.07, 140.39,

134.91, 131.29, 130.55, 129.72, 128.98, 128.82, 128.56, 128.38, 128.18, 128.01, 125.86, 124.35, 119.31, 117.41, 116.74.

2,6-Dihydro-2-(3-((2-hydroxynaphthalen-1-yl)diazenyl)phenyl)-3,4-diphenyl-7H-pyrazolo[3,4-d]pyridazin-7-one (7b). Yield: 70 %; m.p. 234–235 °C. Anal. Calcd. for $C_{33}H_{22}N_6O_2$: C, 74.14; H, 4.15; N, 15.72 %. Found: C, 73.98; H, 4.18; N, 15.73 %. IR (KBr, cm^{-1}): 3362 and 3170 (NH and OH), 3061 and 3027 (Ar CH), 1665 (amide C=O), 1606–1476 (Ar C=C and C=N). 1H -NMR (400 MHz, $DMSO-d_6$, δ / ppm): 8.25 (1H, *br s*, NH), 5.56–5.23 (1H, *br s*, OH), 7.31–6.90 (20H, *m*, ArH). ^{13}C -NMR (100 MHz, $DMSO-d_6$, δ / ppm): 156.80 (amide C=O), 156.68 (ArC–OH), 156.59 and 144.09 (ArC–N=N), 142.54 (pyrazole C–3), 140.66 (pyrazole C–5), 140.29, 140.08, 134.80, 134.67, 131.08, 130.94, 130.87, 130.41, 130.15, 129.75, 129.49, 129.41, 129.23, 128.73, 128.58, 128.26, 128.18, 127.81, 121.95, 122.30, 117.15, 116.84, 113.80.

EXPERIMENTAL

The chemical compounds used in this research were of analytical grade purity and the solvents were purified using appropriate purifying agents and distillation. All melting points were measured using a Barnstead Electrothermal 9200 apparatus, and are reported uncorrected. The IR spectra of the compounds in KBr pellets were recorded on a Mattson 1000 FT–IR spectrometer. The 1H -NMR and ^{13}C -NMR spectra were recorded on Bruker DPX-400, (400 MHz), and high performance digital FT–NMR (100 MHz) spectrometers. The mass spectra were obtained using Varian Mat III 80 eV spectrometer. At the end of the each experiment, TLC was performed using DC Alufolien Kieselgel 60F/254 Merck and a Camag TLC device. The elemental analyses were performed on a Leco CHNS-932 instrument.

General procedure for the syntheses of compounds 2a–f, 3a,b, 6a–c and 7a,b

To an aqueous solution of sodium acetate (3.0 g, 37 mmol) was added 2 ml HCl and then 1 mmol the required amine compound. Subsequently, ethanol was added until complete dissolution. The prepared solution was cooled to 0 °C on an ice bath. To this solution, a solution of 1.2 mmol $NaNO_2$ in 2 ml water was slowly added taking care that the temperature did not exceed 5 °C. Thus, the diazonium salt solution was prepared.

An aromatic or β -dicarbonyl compound (1 mmol) was dissolved in a sufficient amount of ethanol, then cooled and added dropwise into the prepared diazonium salt solution. The resulting colored precipitate was filtered under vacuum and the crude product purified by crystallization from an ethanol–water mixture.

Synthesis of 4-benzoyl-1-(3-bromophenyl)-5-phenyl-1H-pyrazole-3-carboxylic acid (4a)

CuBr solution was prepared according to the procedure given in literature²² and was slowly added by stirring continuously into the diazonium salt solution of compound **1** (prepared as described in the general procedure). The resulting colored precipitate was filtered and purified by crystallization from ethanol–water mixture (9:1).

Synthesis of 4-benzoyl-1-(3-cyanophenyl)-5-phenyl-1H-pyrazole-3-carboxylic acid (4b)

A CuCN + KCN solution, which had been prepared in accordance with a procedure given in the literature,²² was cooled to 0 °C and added dropwise under continuous stirring into a diazonium salt solution of compound **1** (prepared as described in the general procedure). Following the addition, the cold mixture is allowed to warm up to room temperature. When

the temperature reached about 15 °C, the formation of nitrogen gas began. Then the solution was placed on a steam bath and heated at 50 °C for 15 min to complete the decomposition. The pH was adjusted to 3–4 and left for 12 h at room temperature; the resulting precipitate was filtered under vacuum and dried. The residue was purified by crystallization from an ethanol–water mixture (8:2).

Synthesis of 4-benzoyl-1-(3-iodophenyl)-5-phenyl-1H-pyrazole-3-carboxylic acid (4c)

KI (0.166 g, 1 mmol) was dissolved in 10 ml water and the solution was cooled to 0 °C. Then, it was added dropwise under continuous stirring into a diazonium salt solution of compound **1**, which had been prepared in accordance with the general procedure. The pH was adjusted to 3–4 and after standing for 12 h at room temperature, the resulting colored precipitate was filtered under vacuum and purified by crystallization from an ethanol–water mixture (8:2).

Synthesis of 4-benzoyl-1-(3-hydroxyphenyl)-5-phenyl-1H-pyrazole-3-carboxylic acid (4d)

A diazonium salt solution of **1** was prepared according to the general procedure. This solution was brought to room temperature and then heated in a steam bath at 100 °C to allow for the release of nitrogen gas (approximately 15 min). Then some more water was added to the mixture and the pH adjusted to 4. The solution was kept for about 24 h. The formed yellow-colored precipitate was collected by filtration and purified by crystallization from an ethanol–water mixture (9:1).

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ИЗВОД

СИНТЕЗА НОВИХ ДЕРИВАТА 1-(3-АМИНО-ФЕНИЛ)-4-БЕНЗОИЛ-5-ФЕНИЛ-1H-ПИРАЗОЛ-3-КАРБОКСИЛНЕ КИСЕЛИНЕ

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Синтеза 4-бензоил-1-(3-аминофенил)-5-фенил-1H-пиразол-3-карбоксилне киселине (**1**) извршена је према поступку описаном у литератури.¹ Производ 2-(3-аминофенил)-3,4-дифенил-2H-пиразол[3,4-d]пиридазин-7(6H)-он (**5**) добијен је циклокондензационом реакцијом киселине **1** и хидразин-хидрата. Нови пиразолски деривати добијени су реакцијом **1** и **5** са β-дикетонима, β-кетоестрима, β-нафтолом, фенолом и другим реагенсима. Добијена једињења окарактерисана су ¹H-NMR, ¹³C-NMR, ИС и MS спектрима и микроанализом.

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