ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Synthesis of Some New Heterocycles Derived from 3-Amino-5-hydrazinopyrazole dihydrochloride.

Hassan A Etman*, Mahmoud G Sadek, and Abdel-Galil M Khalil.

Department of Chemistry, Faculty of Science, Mansoura University, ET-35516 Mansoura, Egypt.

ABSTRACT

Interaction of 3(5)-amino-5(3)-hydrazinopyrazole dihydrochloride (**1**) with two moles aromatic aldehydes, 2-acetylferrocene, ninhydrin and/or 3,5-diphenylcyclohex-2-enone afforded the corresponding condensation products **3**-**6**. Cyclocondensation of **1** with two moles of α-arylhydrazono acetyl acetone **7** and ethyl α-arylhydrazono acetoacetate **9** was carried out in EtOH:H_2O mixture (1:1) or H_2O to give the corresponding fused pyrazol-1'-ylpyrazolopyrimidine derivatives **8** and **10**. Also, the reaction of **1** with cyclic β-ketoester e.g. diethyl 4-hydroxy-4-methyl-6-oxo-2-(*p*-anisyl)cyclohexane-1,3-dicarboxylate **11** was investigated and the isolated product identified as cyclohexenopyrimidopyrazole derivative **12**. The structures of the new synthesized compounds were elucidated and confirmed by elemental analyses and spectral data.

Keywords: malononitrile, hydrazine hydrate, Schiff base, 2-acetylferrocene, ninhydrin, 3,5-diphenylcyclohex-2-enone.

.

Corresponding author

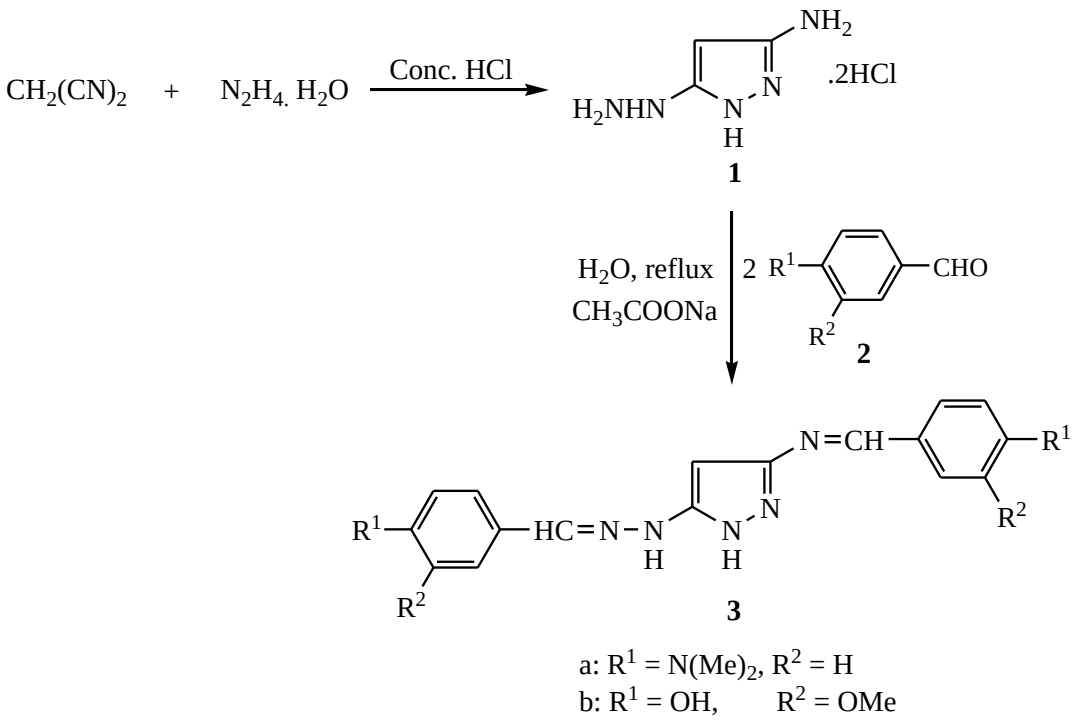
ISSN: 0975-8585

INTRODUCTION

Pyrazole derivatives have attracted continuing interest over the years because of their varied biological and pharmacological activities [1-3] Particularly, aminopyrazole derivatives have been reported as protein β-sheet stabilizers [4] and are largely used as ideal precursors for the synthesis of biologically active fused heterocyclic compounds [5-8]. Some of the 3-aminopyrazole analogues and also find application in photography [9,10] and in the dyestuff industry [11-15]. The chemistry of aminopyrazoles has been recently reviewed and received considerable attention not only from the point of pharmaceutical and medicinal applications but also from their synthetic importance as versatile precursor for the synthesis of azoloazines [16-19]. Literature survey revealed the synthetic strategy required to prepare 3(5)-aminopyrazoles involves either the reactions of hydrazine hydrate with each of α,β-unsaturated nitriles [20-21] and 3-oxoalkanenitriles [22-24], or the reactions of hydrazonyl halides with active methylene nitriles [25]. In the light of these facts, we report herein an efficient synthesis of some new substituted pyrazole compounds via condensation of 3-amino-5-hydrazinopyrazole dihydrochloride with different reagents.

RESULTS AND DISCUSSION

The aminopyrazole compounds have been easily obtained by the reaction of nitrile derivatives with hydrazine hydrate, and are very useful as precursors for the synthesis of fused heterocyclic ring systems. The starting compound 3(5)-amino-5(3)-hydrazinopyrazole dihydrochloride (**1**) was obtained by the condensation of hydrazine hydrate and malononitrile [26]. Condensation of 3(5)-amino-5(3)-hydrazinopyrazole dihydrochloride (**1**) with aromatic aldehydes **2** e.g. *p*-N,N-dimethylaminobenzaldehyde and vanillin gave the corresponding hydrazones **3** as inferred from their correct analytical and spectral data. The IR spectrum of **3a** (as example) showed an absorption band at 1642 cm^{-1} due to (C=N) group an addition to two bands at 3226 and 3312 cm^{-1} due to two (NH) groups. The ^1H NMR of **3a** revealed a singlet signal at 3.05 ppm for twelve protons corresponding to four CH_3 groups, a singlet signal at 7.25 ppm due to the olefinic proton (pyrazole ring), two doublet signals at 6.70 and 7.70 ppm due to the aromatic protons and a singlet signal at 8.55 ppm due to the methine protons (CH=N). On the other hand, the mass spectrum of the same compound showed molecular ion peak at m/z = 375 (M^+, 49) which in agreement with molecular formula $C_{21}H_{25}N_7$.

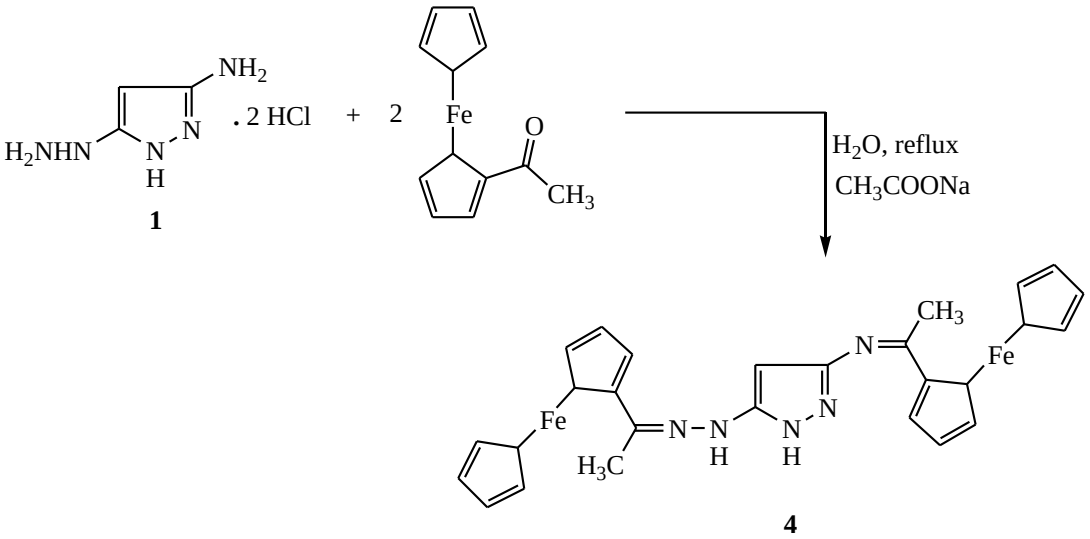


Scheme (1)

The reactivity of **1** towards condensation with aromatic aldehydes prompted us to investigate its behavior towards 2-acetylferrocene. The reaction of **1** with 2-acetylferrocene proceeded in hot water

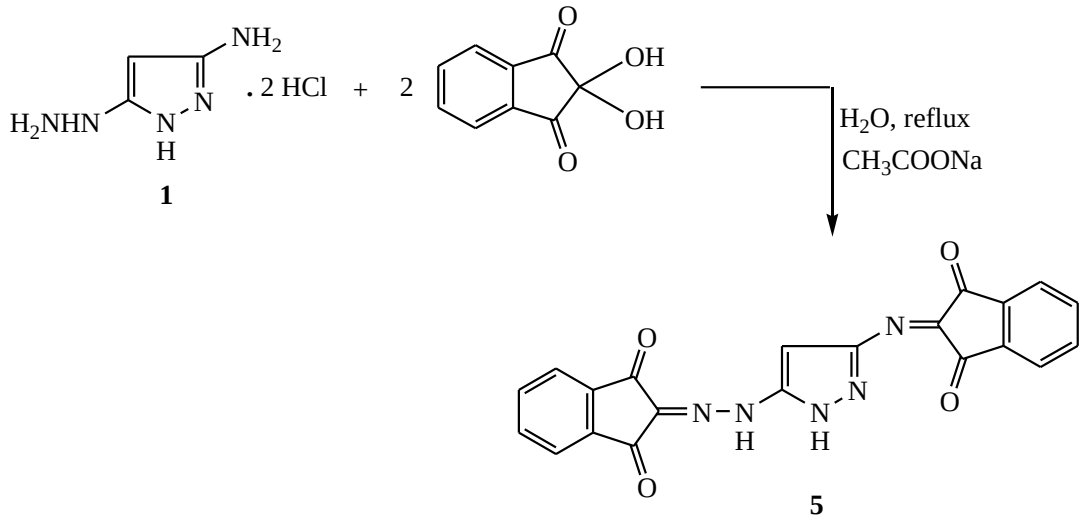
ISSN: 0975-8585

containing sodium acetate to furnish the corresponding Schiff base compound **4**. The chemical structure of **4** was verified by their elemental analyses and spectral data. For example, the IR spectrum showed an absorption peak at 1648 cm^{-1} corresponding to the (C=N) group and a broad absorption peak at 3424 cm^{-1} corresponding to NH groups. Moreover, the mass spectrum showed molecular ion peak at m/z = 533 (M^+, 29) which in agreement with molecular formula $C_{27}H_{27}Fe_2N_5$.



Scheme (2)

The reaction of 3(5)-amino-5(3)-hydrazinopyrazole dihydrochloride (**1**) with two moles of ninhydrin was carried out in hot water and sodium acetate to afford the corresponding condensation product 5-(2-(inden-1,3-dion-2-ylidene)hydrazinyl)-N-(inden-1,3-dion-2-ylidene)-1H-pyrazol-3-amine (**5**). The structure of **5** was verified by elemental analyses and spectroscopic methods. For example, the IR spectrum revealed absorption bands at 1712, 3280 and 3417 cm^{-1} due to the carbonyl and (NH) functions. The ^1H NMR spectrum displayed a singlet signal at signal at 7.15 ppm for olefinic proton (pyrazole ring), a multiplet signal in the region 7.25-7.60 ppm corresponding to the aromatic protons and two singlet signals at 12.70 and 15.85 ppm due to the NH protons. Moreover, the mass spectrum showed molecular ion peak at m/z = 397 (M^+, 18) which in agreement with molecular formula $C_{21}H_{11}N_5O_4$.

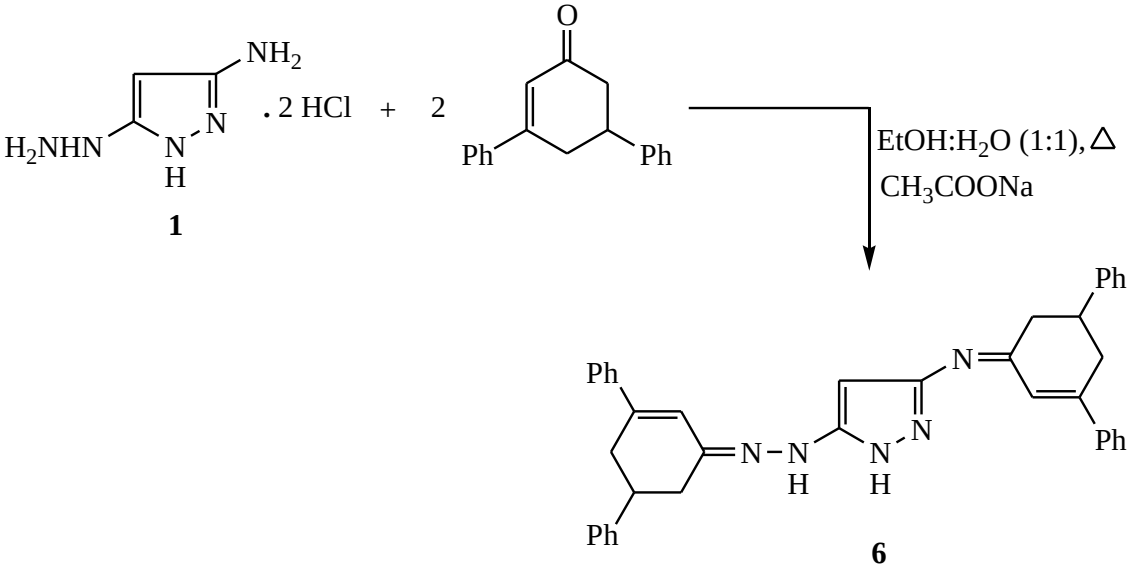


Scheme (3)

The reaction of 3(5)-amino-5(3)-hydrazinopyrazole dihydrochloride (**1**) with two moles of 3,5-diphenylcyclohex-2-enone was carried out under reflux in ethanol-water mixture to furnish the corresponding condensation product **6**. The chemical structure of **6** was elucidated on the basis of its elemental analysis and spectral data. The IR spectrum of displayed absorption bands related to the stretching vibrations of (C=N) and

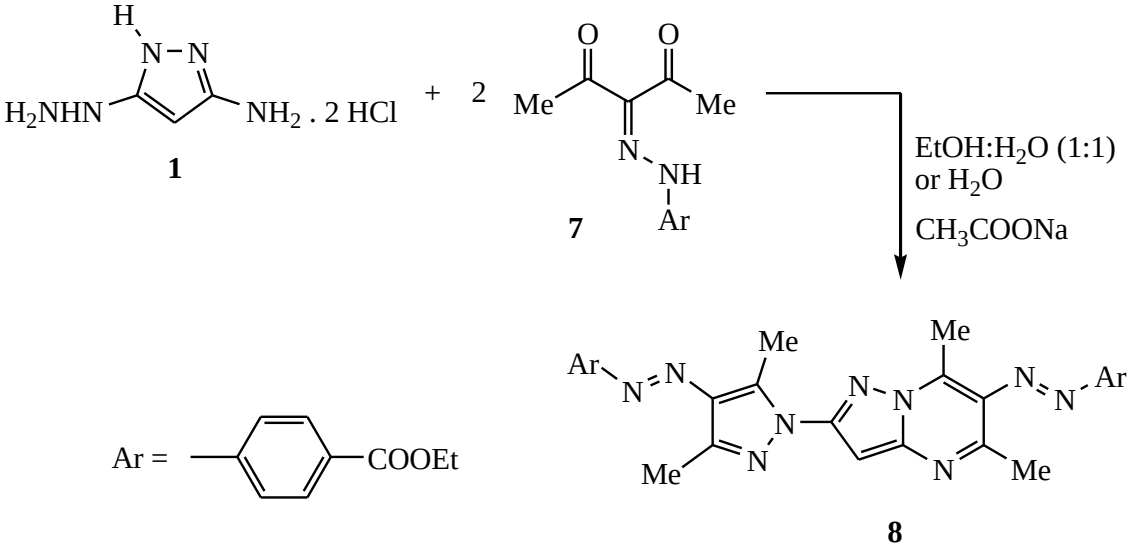
ISSN: 0975-8585

NH groups at 1600 and 3419 cm^{-1}, respectively. The ^1H NMR spectrum exhibited three multiplet signals near 2.38-2.44, 2.78-2.99 and 3.42-3.47 ppm due to protons of the methylene groups (cyclohexene C4-H and C6-H) and methine proton (cyclohexene C5-H). The singlet signal at 6.85 ppm was attributed to the olefinic proton (CH=C, cyclohexene C2-H) while the multiplet signal in the region 7.26-7.56 ppm referred to the aromatic protons and the pyrazole CH=C proton. Mass spectrum showed the molecular ion peak at m/z = 574 (M^+, 37) corresponding to the molecular weight of the molecular formula $C_{39}H_{35}N_5$.



Scheme (4)

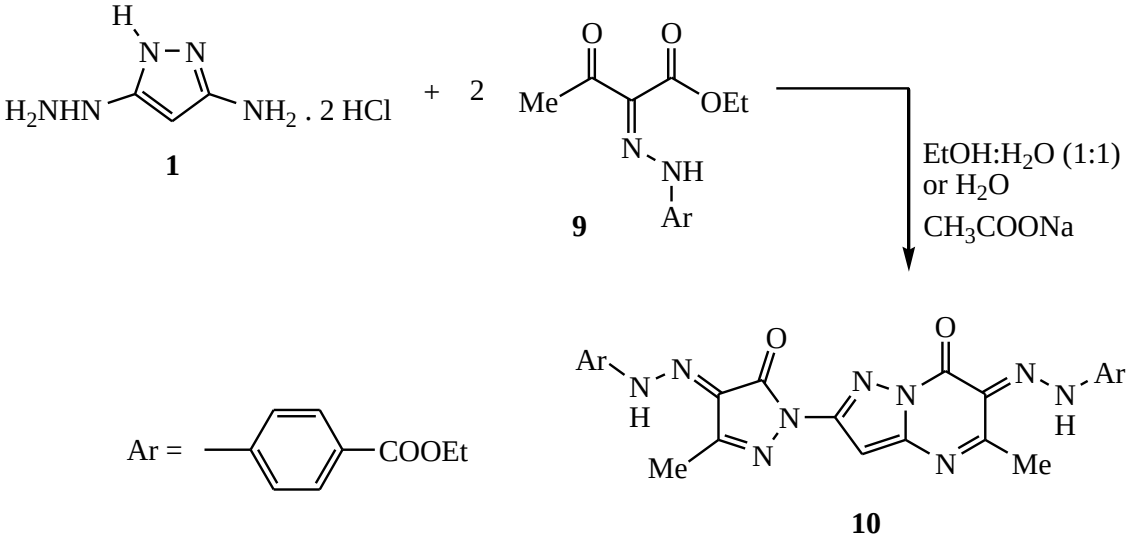
Attempts were made to react 3(5)-amino-5(3)-hydrazinopyrazole dihydrochloride (**1**) with α-arylhydrazono acetyl acetone **7** in THF, MeCN and EtOH with or without NaOAc but no products could be obtained even when the reaction time was extended to 48 h and the starting material was recovered as such. Recently, aqueous mediated reactions have received considerable attention in organic synthesis due to environmental safety reasons. The formation of fused pyrazol-1'-ylpyrazolopyrimidine derivative **8** was established as refluxing two moles of α-arylhydrazono acetyl acetone **7** with **1** in EtOH : H_2O (1:1) or H_2O. The IR spectrum of compound **8** showed an absorption band at 1611 cm^{-1} indicating the presence of C=N group and a broad band at 1718 cm^{-1} due to carbonyl groups (C=O). Its ^1H NMR spectrum displayed a triplet signal at 1.30 ppm due to two methyl protons, two singlet signals at 2.40 and 2.70 ppm due to four methyl protons, a quartet signal at 4.25 ppm due to two methylene protons, a singlet signal at 7.10 due to methine proton (CH=C, pyrazole ring), and a multiplet signal in the region at 7.30-7.65 ppm corresponding to the aromatic protons.



Scheme (5)

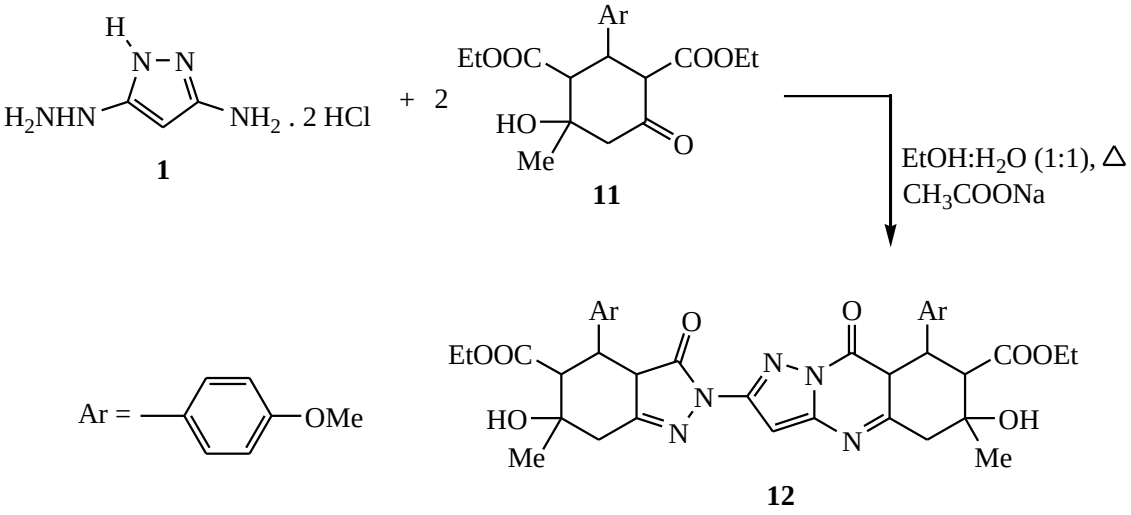
ISSN: 0975-8585

Similarly, The reaction of **1** with ethyl α-arylhydrazono acetoacetate **9** was carried out in s carried out under reflux in EtOH : H_2O (1:1) or H_2O to give the corresponding pyrazol-1'-ylpyrazolopyrimidine derivative **10**.The chemical structure of compound **10** was elucidated on the basis of its elemental analysis and spectral data. The IR spectrum of compound **10** showed absorption bands at 1665 cm^{-1} for the cyclic carbonyl groups, 1718 cm^{-1} due to the carbonyl groups (ester) and 3214 cm^{-1} for the (NH) groups. The ^{1}HNMR spectrum displayed a triplet signal at 1.30 ppm for two methyl protons, two singlet signals at 2.40 and 2.50 ppm for two methyl protons, a quartet signal at 4.25 ppm due to methylene protons, a singlet signal at 7.10 ppm for the methine proton (CH=C, pyrazole ring), a multiplet signal in the region 7.20-7.65 ppm for the aromatic protons and two singlet signals at 12.15 and 13.75 ppm for two NH protons.



Scheme (6)

In connection with the previous successful reactions, it seemed of interest to react 3(5)-amino-5(3)-hydrazinopyrazole dihydrochloride (**1**) with diethyl 4-hydroxy-4-methyl-6-oxo-2-(*p*-anisyl)cyclohexane-1,3-dicarboxylate (**11**) (as cyclic β-ketoester) to give the cyclohexenopyrimidopyrazole derivative **12** on the basis of its correct analytical and spectral data. The IR spectrum of compound **12** showed absorption bands at 1731 cm^{-1} corresponding to the carbonyl groups (C=O) and 3511 cm^{-1} corresponding to hydroxyl groups (OH). Mass spectrum showed the molecular ion peak at m/z = 742 (M^+, 28) corresponding to the molecular weight of the molecular formula $C_{39}H_{43}N_5O_{10}$.



Scheme (7)

ISSN: 0975-8585

EXPERIMENTAL

Melting points were measured on an electrothermal Gallenkamp melting point apparatus. Elemental analyses were carried out at the Microanalytical Unit, Cairo University, Giza, Egypt; the results were in satisfactory agreement with the calculated values. The IR spectra were recorded in KBr disks on a Mattson 5000 FTIR spectrometer (not all frequencies are reported). The NMR spectra were acquired using a Bruker WP 300 spectrometer at 300 MHz using *TMS* as an internal standard and $CDCl_3$ or DMSO-d_6 as solvent. The Mass spectra were performed using a Varian MAT 311 mass spectrometer at 70 eV.

Synthesis of 5-(arylidenehydrazinyl)-N-arylidene-1H-pyrazol-3-amine 3a and 3b:

A mixture of **1** (0.005 mol) in 10 ml water, sodium acetate (0.01 mol) and the aromatic aldehyde (namely: 4-N,N-dimethylaminobenzaldehyde and vanillin, 0.01 mol) in ethanol (30 ml) was refluxed for 2 hours. The solid product obtained on cooling was filtered off and recrystallized from ethanol to give **3a** and **3b**.

5-(2-(4-N,N-Dimethylaminobenzylidene)hydrazinyl)-N-(4-N,N-dimethyl-aminobenzylidene)-1H-pyrazol-3-amine (3a):

m.p. = 222-224°C. Yield = 74%. IR ($\overline{\nu}$ /cm-1): 1642 (C=N), 3226 (NH), 3312 (NH). 1H NMR (DMSO): δ/ppm = 3.05 (s, 12H, 4CH3), 6.70 (d, 4H, Ar-H), 7.25 (s, 1H, CH=C), 7.70 (d, 4H, Ar-H), 8.55 (s, 2H, 2CH=N). MS (M+; EI): m/z (%) = 375 (49). Analysis for C21H25N7 (375.47): Calcd.: C, 67.18; H, 6.71; N, 26.11; Found: C, 67.32; H, 6.77; N, 26.02.

5-(2-(4-Hydroxy-3-methoxybenzylidene)hydrazinyl)-N-(4-hydroxy-3-methoxybenzylidene)-1H-pyrazol-3-amine (3b):

m.p. = 188-189°C. Yield = 82%. IR ($\overline{\nu}$ /cm^{-1}): 1638 (C=N), 3175 (OH), 3248 (NH), 3334 (NH). ^{1}H NMR ($CDCl_3$): δ/ppm = 3.80 (s, 6H, 2OCH_3), 7.10 (s, 1H, CH=C), 7.20-7.60 (m, 6H, Ar-H), 8.50 (s, 2H, 2CH=N), 8.90 (s, 2H, 2OH), 13.10 (s, 1H, NH), 14.50 (s, 1H, NH). Analysis for $C_{19}H_{19}N_5O_4$ (381.39): Calcd.: C, 59.84; H, 5.02; N, 18.36; Found: C, 59.69; H, 5.09; N, 18.46.

Condensation of 1 with 2-acetylferrocene: Synthesis of Schiff base (4):

A mixture of **1** (0.005 mol) in 10 ml water, sodium acetate (0.01 mol) and 2-acetylferrocene (0.01 mol) in ethanol (30 ml) was refluxed for 4 hours. The solid product obtained on cooling was filtered off and recrystallized from ethanol to give **4**.

m.p. = 210-211°C. Yield = 64%. IR ($\overline{\nu}$ /cm^{-1}): 1648 (C=N), 3424 (NH). MS (M^+; EI): m/z (%) = 533 (29). Analysis for $C_{27}H_{27}Fe_2N_5$ (533.23): Calcd.: C, 60.82; H, 5.10; N, 13.13; Found: C, 60.58; H, 5.18; N, 13.02.

Synthesis of 5-(2-(inden-1,3-dion-2-ylidene)hydrazinyl)-N-(inden-1,3-dion-2-ylidene)-1H-pyrazol-3-amine (5):

To a solution of **1** (0.005 mol) in 30 ml water-ethanol mixture (1:2), sodium acetate (0.01 mol) and ninhydrin (0.01 mol) were added. The reaction mixture was refluxed for 5 hours and the solid product which obtained on cooling was filtered off and recrystallized from ethanol.

m.p. = 273-274°C. Yield = 58%. IR ($\overline{\nu}$ /cm^{-1}): 1617 (C=N), 1712 (broad, C=O groups), 3280 (NH), 3417 (NH). ^{1}H NMR (DMSO): δ/ppm = 7.15 (s, 1H, CH=C), 7.25-7.60 (m, 8H, Ar-H), 12.70 (s, 1H, NH), 15.85 (s, 1H, NH). MS (M^+; EI): m/z (%) = 397 (18). Analysis for $C_{21}H_{11}N_5O_4$ (397.34): Calcd.: C, 63.48; H, 2.79; N, 17.63; Found: C, 63.63; H, 2.84; N, 17.56.

Synthesis of 5-(2-(3,5-diphenylcyclohex-2-enylidene)hydrazinyl)-N-(3,5-diphenylcyclohex-2-enylidene)-1H-pyrazol-3-amine (6):

A mixture of **1** (0.005 mol), 3,5-diphenylcyclohex-2-enone (0.01 mol) and sodium acetate (0.01 mol) in 30 ml ethanol-water mixture (1:1) was refluxed for 4 hours. The solid precipitate that obtained on cooling was

filtered off, dried and recrystallized from ethanol to give **6**.
m.p. = 155-156°C. Yield = 71%. IR ($\bar{\nu}$ /cm^{-1}): 1600 (C=N), 3419 (NH). ^{1}H NMR (DMSO): δ/ppm = 2.38-2.44 (m, 4H, 2C$_4$-H), 2.78-2.99 (m, 4H, 2C$_6$-H), 3.42-3.47 (m, 2H, 2C$_5$-H), 6.85 (s, 2H, 2C$_2$-H), 7.26-7.56 (m, 21H, Ar-H and prazole CH=C). MS (M$^+$; EI): m/z (%) = 574 (37). Analysis for $C_{39}H_{35}N_5$ (573.73): Calcd.: C, 81.64; H, 6.15; N, 12.21; Found: C, 81.47; H, 6.08; N, 12.32.

Synthesis of 5,7-dimethyl-6-(4-carboethoxyphenylazo)-2-(3,5-dimethyl-4-(4-carboethoxyphenylazo)-1H-pyrazol-1-yl)pyrazolo[1,5-a]-pyrimidine (8):

To H_2O (20 ml) or H_2O-EtOH mixture (20 ml, 1:1) were added 3(5)-amino-5(3)-hydrazinopyrazole dihydrochloride (**1**) (0.005 mol), sodium acetate (0.01 mol) and α-arylhydrazono acetyl acetone **7** (0.01 mol). The reaction mixture was refluxed for 8 hours. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and extracted using 2 × 30 ml portions of ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to give a residual mass. The residue obtained on cooling was recrystallized from EtOH-DMF mixture (1:1) to give the target compound **8**.
m.p. = 234-235°C. Yield = 62%. IR ($\bar{\nu}$ /cm^{-1}): 1611 (C=N), 1718 (broad, C=O groups). ^{1}H NMR (DMSO): δ/ppm = 1.30 (t, 6H, 2CH$_3$), 2.40 (s, 6H, 2CH$_3$), 2.70 (s, 6H, 2CH$_3$), 4.25 (q, 4H, 2CH$_2$), 7.10 (s, 1H, CH=C), 7.30-7.65 (m, 8H, Ar-H). Analysis for $C_{31}H_{31}N_9O_4$ (593.64): Calcd.: C, 62.72; H, 5.26; N, 21.24; Found: C, 62.88; H, 5.34; N, 21.32.

Synthesis of 5-methyl-6-(4-carboethoxyphenylhydrazono)-2-(3-methyl-5oxo-4-(4-carboethoxy phenyl hydrazono)-1H-pyrazol-1-yl)-pyrazolo[1,5-a]pyrimidin-7-one (10):

A mixture of 3(5)-amino-5(3)-hydrazinopyrazole dihydrochloride (**1**) (0.005 mol), sodium acetate (0.01 mol) and ethyl α-arylhydrazono acetoacetate **9** (0.01 mol) in H_2O (20 ml) or H_2O-EtOH mixture (20 ml, 1:1) was refluxed for 8 hours. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and extracted using 2 × 30 ml portions of ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to give a residual mass. The residue obtained on cooling was recrystallized from EtOH-DMF mixture (1:1) to give the target compound **10**.

m.p. = 252-253°C. Yield = 56%. IR ($\bar{\nu}$ /cm^{-1}): 1615 (C=N), 1718 (broad, C=O groups), 1665 (broad, cyclic C=O), 3214 (NH). ^{1}H NMR (DMSO): δ/ppm = 1.30 (t, 6H, 2CH$_3$), 2.40 (s, 3H, CH$_3$), 2.50 (s, 3H, CH$_3$), 4.25 (q, 4H, 2CH$_2$), 7.10 (s, 1H, CH=C), 7.20-7.65 (m, 8H, Ar-H), 12.15 (s, 1H, NH), 13.75 (s, 1H, NH). Analysis for $C_{29}H_{27}N_9O_6$ (597.58): Calcd.: C, 58.29; H, 4.55; N, 21.10; Found: C, 58.10; H, 4.46; N, 21.22.

Synthesis of ethyl 2-(5-(ethoxycarbonyl)-3,3a,4,5,6,7-hexahydro-6-hydroxy-4-(4-methoxyphenyl)-6-methyl-3-oxoindazol-2-yl)-5,6,7,8,8a,9-hexahydro-6-hydroxy-8-(4-methoxyphenyl)-6-methyl-9-oxo-pyrazolo[5,1-b]quinazoline-7-carboxylate (12):

To a solution of **1** (0.005 mol), diethyl 4-hydroxy-4-methyl-6-oxo-2-(*p*-anisyl)cyclohexane-1,3-dicarboxylate (**11**) (0.01 mol) and sodium acetate (0.01 mol) in 30 ml ethanol-water mixture (1:1) was refluxed for 6 hours. The solid precipitate obtained on cooling was filtered off, dried and recrystallized from ethanol to give **12** as yellow crystals.

m.p. = 261-262°C. Yield = 62%. IR ($\bar{\nu}$ /cm^{-1}): 1731 (broad, C=O groups), 3511 (OH groups). MS (M$^+$; EI): m/z (%) = 742 (28). Analysis for $C_{39}H_{43}N_5O_{10}$ (741.79): Calcd.: C, 63.15; H, 5.84; N, 9.44; Found: C, 62.94; H, 5.75; N, 9.57.

REFERENCES

[1] Rutavichyus AI, Valyulene SP, Mozolis V. J Org Chem 1987; 1083.
[2] Singh SP. Heterocycles 1990;31:855.
[3] Sternbach LM, Prog Drug Res 1978;22:229.
[4] Kirsten CN, Schrader TH. J Am Chem Soc 1997;119:12061.
[5] Ghiron C, Nencini A, Micco I, Zanaletti R, Maccari L, Bothmann H, Haydar S, Varrone M, Pratelli C, Harrison B. Int Patent Appl. WO=2008=087529 (2008).

[6] Soma S, Bikash D, Anindya B, Shovanlal G, Kolluru S, Tarun J. Eur J Med Chem 2006;41:1190.
[7] Alexandre VI, Dmitri ED, Elena SG, Elena SD, Madina GK, Angela GK, Volodymyr MK, Oleg DM, Sergey ET, Ilya MO, Anton AV. Bioorg Med Chem Lett 2010;20:2133.
[8] Kim I, Jong HS, Chang MP, Joon WJ, Hyung RK, Jin RH, Zaesung N, Young-Lan H, Young SC, Nam K, Dong JJ. Bioorg Med Chem Lett 2010;20: 922.
[9] David DR. British Patent 1,491,604 (1977).
[10] Brooker W. US Patent 2,646,409 (1953).
[11] Helal MH, Elgemeie GH, Masoud DM. Pigm Resin Technol 2007;36:306.
[12] Ho YW. Dyes Pigments 2005; 64: 223.
[13] Karcı F, Demircalı A. Dyes Pigments 2007;74: 288.
[14] Sayed AZ, Aboul-Fetouh MS, Nassar HS. J Mol Struc 2012;1010:146.
[15] Rizk HF, El-Badawi MA, S.A. Ibrahim SA, M.A. El-Borai MA. Arab J Chem 2011;4:37.
[16] Aggarwal R, Kumar V, Kumar R, Singh SP. Beilstein J Org Chem 2011;7:179.
[17] Lee KY, Kim JM, Kim JN. Tetrahedron Lett 2003;6737.
[18] Elmaati TMA, El-Taweel FM. J Heterocycl Chem 2004; 41: 109.
[19] Anwar HF, Elnagdi MH. Arkivoc 2009;(i):198.
[20] Sadek KU, Ali Selim M, Elnagdi MH, Otto HH, Bull Chem Soc Jpn 1993;66:2927.
[21] (a) Cai J, Jiang H, Lin X. Huagong Shikan 2006;20:15. (b) Ege G, Franz H. J Heterocycl Chem 1982;19:1267.
[22] Pask CM, Camm KD, Kilner CA, Halcrow MA. Tetrahedron Lett 2006;47:2531.
[23] Elnagdi MH, El-Moghayar MRH, Fleita DH, Hafez EAA, Fahmy SM. J Org Chem 1976;41:3781.
[24] Riyadh SM, Al-Matar HM, Elnagdi MH. Molecules 2008;13:3140.
[25] Shawali AS, Hassaneen HM. Tetrahedron 1973;29:121.
[26] Gray EJ, Stevens HNE, Stevens MFG. J Chem Soc, Perkin Trans 1 1978;885.