Article

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Pyrazolones as Building Blocks in Heterocyclic Synthesis: Synthesis of New Pyrazolopyran, Pyrazolopyridazine and Pyrazole Derivatives of Expected Antifungicidal Activity

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A series of new pyrazolone and pyrazole derivatives with expected antifungicidal activity have been prepared through the reactions 3-phenyl-1-*H*-pyrazol-5(4*H*)-one (**3**) and 4-(dimethylaminomethylene)-3-phenyl-1*H*-pyrazol-5(4*H*)-one (**5**) with a variety of electrophilic reagents and nucleophilic reagents. The newly synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral studies.

Keywords: Pyrazolone; Pyrazolopyran and pyrazolopyridazine and pyrazole derivatives.

INTRODUCTION

Heterocycles, containing the pyrazolone nucleus, have attracted much attention due to their interesting biological activities.[1–4] The synthesis of a large number of heterocycles containing pyrazolone nucleus led to very interesting and useful antitumorally,[5] antibacterially,[6] and agrochemically active products.[7] Pyrazolone-5 derivatives form an important class of organic compounds and represent a major scientific and applied interest in biological, analytical applications, catalysis, dye and extraction metallurgy.[8–11] Furthermore, they have the potential to form different types of coordination compounds due to the several electron-rich donor centers.[12,13] Well-known medicinal pyrazolone dipyrone, has shown to inhibit the activities in a dose-dependent manner of cyclooxygenase enzyme COX-1 and its variant COX-3,[14] which catalyze the rate-limiting step of prostaglandin synthesis. Pyrazolones are also well-known as an active moiety in the class of NSAIDs and used in the treatment of arthritis, musculo skeletal and joint disorder.[15–16] 5-Pyrazolone derivatives are widely used in medical practice (antipyrine, amidopyrine, analgin, etc.).[17] Most of the compounds belonging to this series of drugs are characterized by the presence of phenyl substituents in position 1 of the pyrazoline ring. Thus, the biological activities of pyrazol-5-ones depend on the nature of the substituents.[18] On the other hand, the chemistry of pyrazole derivatives received great attention due to their biological activities as potential HIV-1 inhibitors,[19] insecticides,[20] fungicides,[20] antiviral agents,[21] and due to their anticancer activity.[22] Also, the chemistry of fused pyrazoles such as pyrazolopyrimidines and related fused heterocycles has drawn great attention due to the pharmacological importance and their structural resemblance to purines.[23] Several substituted pyrazolo-pyrimidine derivatives demonstrated significant antimicrobial[24] and antiviral activities,[25] also they have been identified as adenosine antagonists, tyrosine kinase, and Src-kinase inhibitors.[26–30] In continuation of this work and as apart of our biological chemistry programme,[31–33] we report here the utility of 3 in the synthesis of unique heterocycles of expected biological interest.

RESULTS AND DISCUSSION

It has been reported that ethyl benzoylacetate (**1**) reacted with hydrazine hydrate in domestic microwave oven to yield the pyrazolone derivative **3** *via* intermediacy of hydrazide derivative **2**.[34] Trials to isolate the acyclic intermediate **2** were failed under a variety of mild conditions (Scheme I).

Pyrazol-5-one derivative **3** was exploited as a key intermediate for the synthesis of hitherto unknown fused pyrazoles through its reaction with some reagents. Thus, fusion of pyrazolone **3** with dimethylformamide dimethyl

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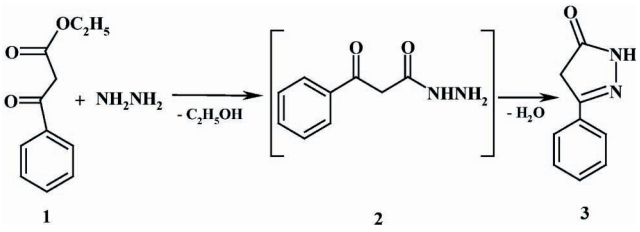
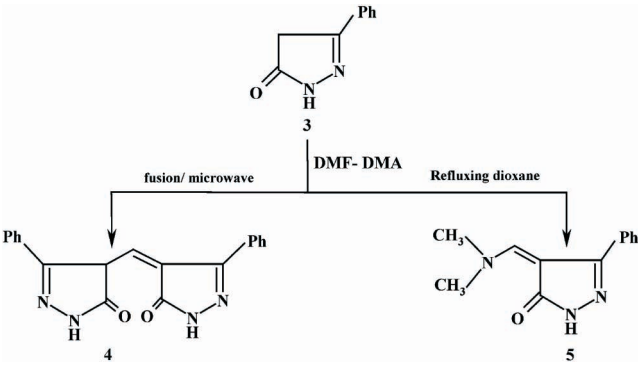
Scheme I



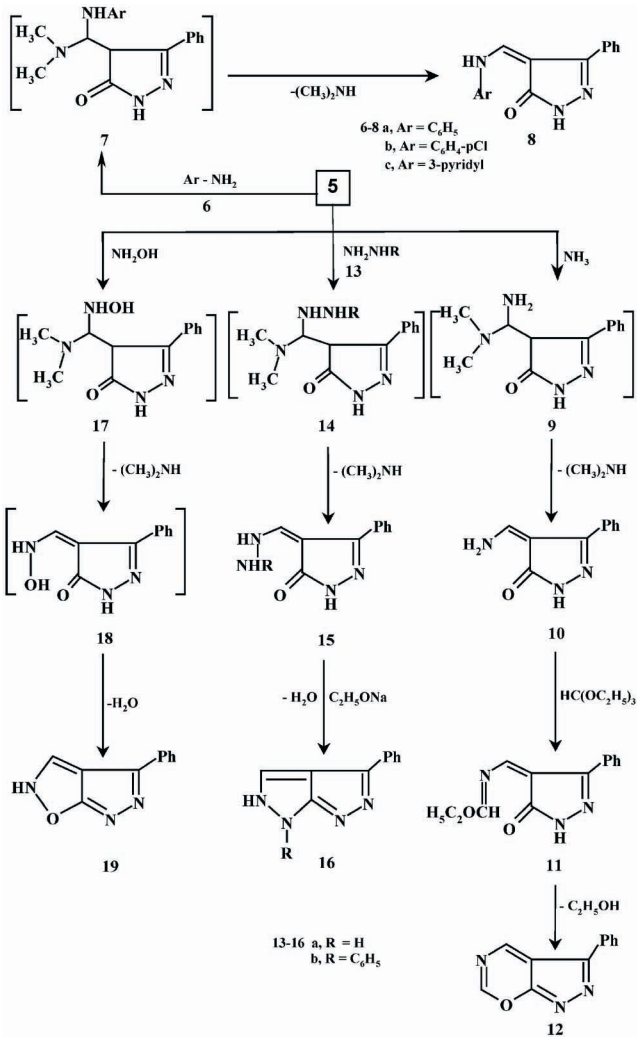
acetal (DMF-DMA) in domestic microwave oven afforded the pyrazolone **4**. Establishing structure **4** was based on its spectral analyses. The mass spectrum of **4** showed a molecular ion peak at *m/z* = 330 in agreement with its molecular formula $C_{19}H_{14}N_4O_2$. Refluxing prazolone **3** with dimethylformamide dimethyl acetal in dry dioxane for about 6 hrs afforded the pyrazolone derivative **5**. Establishing structure **5** was based on its elemental analyses and spectral data. Thus, ^{1}H NMR spectrum of compound **5** revealed an intense singlet signal at δ = 3.25, 3.29 ppm corresponding to two methyl functions, the olifinic proton and NH group appeared as two singlet signals at δ = 7.31 and 10.87 ppm respectively. The ^{13}C NMR data of compounds **5** showed chemical shift values conform to the suggested structure. The mass spectrum of the same compound is in accordance with the proposed structure. Thus, it showed a very intense molecular ion peak at *m/z* 215 and a number of fragments agree with the proposed structure (Scheme II).

Compound **5** was examined as a key precursor toward a variety of nucleophilic reagents aiming at exploring its synthetic potentiality. Thus, when compound **5** is allowed to reflux with aniline **6** in ethanol containing a catalytic amount of piperidine, pyrazolone derivative **8a** was obtained *via* intermediacy of **7**. Similarly, anilines **6b,c** reacted with **5** to give pyrazolones **8b,c** respectively (Scheme III). The structure of the latter product **8** was established on the basis of its elemental analysis and spectral data. For example, the mass spectrum of **8a** showed a molecular ion peak at *m/z* = 263 in agreement with its molecular formula $C_{16}H_{13}N_3O$. The reactivity of **5** towards some nitrogen nucleophiles was investigated. Thus, when **5** was treated with ammonia, the transamination adduct **10** was formed in a good yield *via* intermediacy of **9**.[35] Treatment of **10** with triethylorthoformate in refluxing acetic anhydride for 3 hr afforded Ethyl *N*-((5-oxo-3-phenyl-1*H*-pyrazol-4(5*H*)ylidene)methyl)-formimidate (**11**) which could be cyclized to 3-phenylpyrazolo[4,3-*e*][1,3]oxazine (**12**), upon boiling in pyridine. Structures of compounds **11** and **12** were estab-

Scheme II



Scheme III



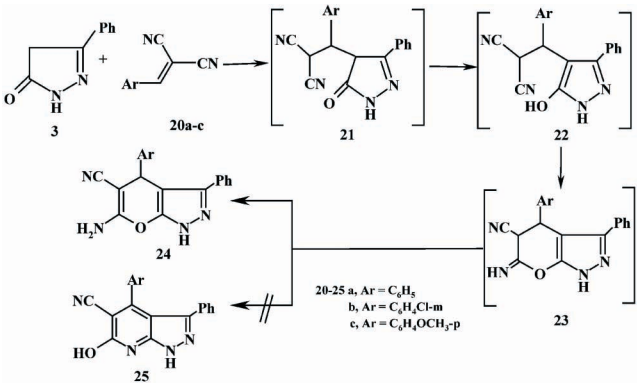
lished on the basis of elemental analysis and spectral data. For example, the ^{1}H NMR of compound **11** showed a triplet at δ = 1.22 ppm and quarter at δ = 3.61 ppm corresponding to ethyl function, while the aromatic and alkenyl protons appeared as multiples at δ = 7.43-7.53, and a single singlet at δ = 12.84 corresponds to NH group. The IR spectrum of **12** was free from the absorption bands for carbonyl and amino groups and the ^{1}H NMR of **12** revealed only the signals for the aromatic proton at δ = 7.46-9.76 (Scheme III).

Treatment of pyrazolone **5** with hydrazine and phenyl hydrazine in refluxing ethanol afforded the acyclic hydrazide derivatives **15a,b** respectively. Establishing structure **15** was based on its elemental analyses and spectral data. For example, the ^{1}H NMR of **15a** revealed the presence of singlet signal at δ = 5.95 ppm corresponding to the olifinic protons and a multiplet signal at δ = 7.32-7.74 ppm corresponding to aromatic protons and the amine proton appeared as a singlet signal at δ = 8.53 ppm.

Treatment of **15a,b** with sodium ethoxide solution afforded the cyclic pyrazolo[3,4-*c*]pyrazole **16a,b** (Scheme III). Establishing structure **16** was based on its elemental analyses and spectral data. For example, the IR spectrum of **16a** revealed the absence of carbonyl group indicating that compound **16** is formed from **15** *via* tautomerism, cyclization and subsequent elimination of water molecule. The mass spectrum of the same product is in accordance with the proposed structure. The reaction of hydroxyl amine with pyrazolone **5** in refluxing pyridine afforded the fused isoxazole **19**. Formation of **19** from the reaction of pyrazolone **5** and hydroxyl amine is believed to be formed *via* initial addition of hydroxyl amine to the double bond system of **5** to give the intermediate **17** that loses diethyl amine giving the non isolable intermediate **18** that loses water to give isoxazole **19** (Scheme III). Establishing structure **19** was based on its elemental analysis and spectral data.

The foregoing results prompt us to investigate the synthetic potentiality of pyrazolone **3** toward a variety of electrophilic reagents as potential precursors for fused heterocyclic systems. Thus, treatment of pyrazolone **3** with arylidenemalononitrile **20** in refluxing ethanol containing a catalytic amount of piperidine afforded either pyranopyrazole derivative **24** or its isomeric pyrazolo-pyridine **25** (Scheme IV). Structure **25** was ruled out and structure **24** was established as a sole reaction product based on its spectral

Scheme IV

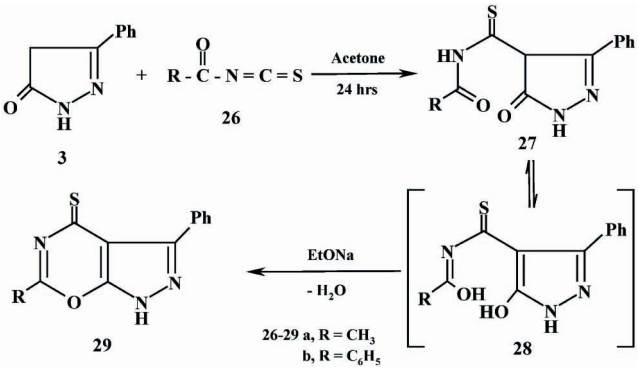


data. For example the IR spectrum of compound **24a** revealed the absence of OH group absorption band, in addition it revealed the presence of an amino function at ν_{max} = 3367 and 3300 cm^{-1}. The ^{1}H NMR spectrum showed a singlet signal at δ = 5.22 ppm corresponding to H-4 pyran, a multiplet signals at δ = 7.01-7.64 ppm corresponding to aromatic protons and NH_2 and a singlet signal at δ = 11.82 characteristic of NH group. Formation of **24** is believe to be formed *via* initial addition of the methylene group of **3** on the double bond of the arylidene **20** to give the Michael adduct **21** that underwent tautomerism followed by intramolecular cyclization to give **24**.

The behavior of pyrazolone **3** towards isothiocyanate reagents was also investigated. Thus, the reaction of pyrazolone **3** with acetyl isothiocyanate and benzoyl isothiocyanate **26a,b** respectively in dry acetone for 24 h afforded the acyclic structures **27a,b**. Structures **27a,b** were confirmed by its correct elemental analyses and spectral data. For example, the mass spectrum of compound **27a** revealed the molecular ion peak at *m/z* = 261 (M^+) corresponding to the molecular formula $C_{12}H_{11}N_3O_2S$. Compounds **27a,b** could be cyclized to the corresponding pyrazolo[4,3-*e*] oxazine derivatives **29a,b** *via* intermediacy of **28** upon boiling in sodium ethoxide through elimination of water molecule. The structure of compounds **29a,b** was established on the basis of elemental analyses and spectral data of the isolated reaction product (Scheme V). For example, the IR spectrum of **29a** revealed no absorption bands due to carbonyl groups.

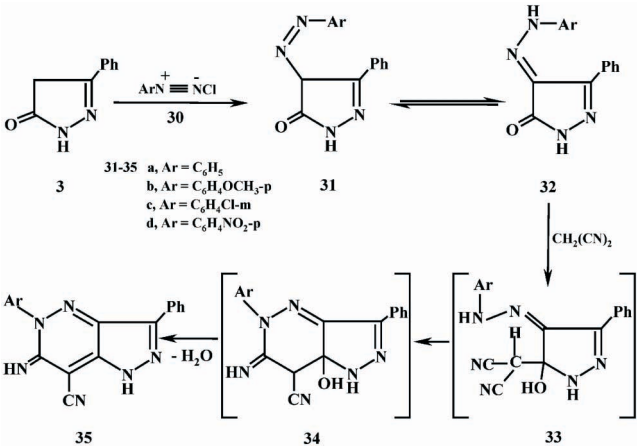
The reaction of pyrazolone **3** with aryl diazonium salts was also investigated. Thus, coupling of **3** with ben-

Scheme V



zenediazonium salt **30a** in ethanol containing sodium acetate afforded the corresponding hydrazone **31a** that tautomerizes into **32a** based on its spectral data. For example, the ^{1}H NMR spectrum of compound **32a** recorded in DMSO-d_6 revealed a signal at δ = 12.11 ppm which could be attributed to hydrazone NH group. Similarly, pyrazolone **3** coupled readily with aryl diazonium chlorides **30b-d** in the same reaction conditions to give the corresponding hydrazones **32b-d**. Fusion of aryl hydrazones **32a** with malononitrile in domestic microwave oven gave a product with a molecular formula $C_{18}H_{12}N_6$ which was considered to be the pyrazolopyridazine derivative **35a**. Formation of **35** is believed to be formed *via* initial addition of malononitrile on the carbonyl group of **32** to give the intermediate **33** which cyclizes into **34** which readily losses a molecule of water to give **35a**. Similarly, aryl hydrazones **32b-d** fused with malononitrile to give pyrazolopyridazine derivatives **35b-d** as demonstrated in Scheme VI.

Scheme VI



CONCLUSION

In conclusion, compounds **3** and **5** were used as efficient precursors for the synthesis of new heterocycles including the pyrazole moiety with expected biological activities.

EXPERIMENTAL

All melting points are uncorrected. IR spectra (KBr) were recorded on a FTIR 5300 spectrometer (ν, cm^{-1}). The ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 at 200 MHz on a Varian Gemini NMR spectrometer (δ, ppm) using TMS as an internal standard. Mass spectra were obtained on GC Ms-QP 1000 EX mass spectrometer at 70 ev. Thin layer chromatography (TLC) was used to monitor the course of reactions and ascertain the purity of compounds, and detection of the components was made by exposure to ultraviolet light. Elemental analyses were carried out by the Micro analytical Research Center, Faculty of Science, Cairo University and Micro analytical Research Center. Compound **3** was prepared following literature procedure.[34]

Preparation of 4-((5-oxo-3-phenyl-1*H*-pyrazol-4(5*H*)-ylidene)methyl)-3-phenyl-1*H*-pyrazol-5(4*H*)-one (4)

A mixture of compound **3** (0.01 mole), DMF-DMA (0.01 mole) and ammonium acetate (0.5 g) was exposed to microwave irradiation (power input 20%) for 4.0 min, the reaction mixture was allowed to reach room temperature, then diluted with ethanol with stirring and the solid product that formed, was filtrated and crystallized from ethanol to give pale red crystals; yield 81%; m.p. 285-286 °C; IR (KBr) ν cm^{-1} 3150 (NH), 3056 (CH arom), 1685, 1730 (2 C=O); ^{1}H NMR (DMSO-d_6) δ = 3.96 (s, 1H, CH), 7.43-7.95 (m, 11H, aromatic and alkenyl H), 9.76 (s, 1H, NH), 12.83 (s, 1H, NH); MS: *m/z* (%) = 330 (M$^+$). *Anal.* Cacld for $C_{19}H_{14}N_4O_2$ (330.34): C, 69.08; H, 4.27; N, 16.96%. Found: C, 69.15; H, 4.35; N, 17.10%.

Preparation of 4-((dimethylamino)methylene)-3-phenyl-1*H*-pyrazol-5(4*H*)-one (5)

To a solution of compound **3** (0.01 mole) in dioxane (30 mL), DMF-DMA (0.01 mole) was added. The reaction mixture was refluxed for 6 hrs. The solid product, so formed, was collected by filtration and crystallized from ethanol to give yellow crystals; yield 76%; m.p. 210-211 °C; IR (KBr) ν cm^{-1} 3432 (NH), 2919 (CH-aliph), 1672

(C=O); ^{1}H NMR (DMSO-d_6) δ = 3.25 (s, 3H, CH_3), 3.29 (s, 3H, CH_3), 7.31 (s, 1H, olifinic proton), 7.37-7.43 (m, 5H, aromatic protons), 10.87 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 43.90, 43.90, 103.50, 127.10, 127.65, 127.65, 128.90, 128.90, 135,70, 145.95, 153.70, 173.25; MS: *m/z* (%) = 215 (M^+). *Anal.* Cacld for $C_{12}H_{13}N_3O$ (215.25): C, 66.96; H, 6.09; N, 19.52%. Found: C, 66.90; H, 6.00; N, 19.60%.

Preparation of compounds (8a-c)

General procedure

Equimolar amounts of compound **5** (0.01 mole) and compounds **6a-c** (0.01 mole) in ethanol (30 mL) containing a few drops of piperidine were refluxed for 12 hrs and poured into cold water (30 mL) and acidified with HCl. The solid product that formed was filtered and crystallized from the proper solvent to give (**8a-c**).

3-Phenyl-4-((phenylamino)methylene)-1*H*-pyrazol-5(4*H*)-one (8a)

It was obtained as yellow crystals from ethanol; m.p. 250-252 °C; yield 68%; IR (KBr) ν cm^{-1} 3138 (NH), 1671 (C=O); ^{1}H NMR (DMSO-d_6) δ = 7.21-7.75 (m, 11H, aromatic protons + alkenyl-H), 8.52 (s, 1H, NH), 11.59 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 102.95, 117.45, 117.45, 123.15, 128.35, 128.35, 128.50, 129.55, 129.55, 130.10, 130.10, 136.55, 140.60, 149.00, 155.10, 173.20; MS: *m/z* (%) = 263 (M^+). *Anal.* Cacld for $C_{16}H_{13}N_3O$ (263.29): C, 72.99; H, 4.98; N, 15.96%. Found: C, 72.90; H, 4.92; N, 15.90%.

4-(((4-Chlorophenyl)amino)methylene)-3-phenyl-1*H*-pyrazol-5(4*H*)-one (8b)

It was obtained as pale yellow crystals from benzene; m.p. 220-222 °C; yield 71%; IR (KBr) ν cm^{-1} 3133 (NH), 1667 (C=O); ^{1}H NMR (DMSO-d_6) δ = 7.46-7.75 (m, 10H, aromatic protons and alkenyl proton), 8.47 (s, 1H, NH), 11.61 (s, 1H, NH); MS: *m/z* (%) = 297 (M^+). *Anal*. Cacld for $C_{16}H_{12}ClN_3O$ (297.74): C, 64.54; H, 4.06; Cl, 11.91; N, 14.11%. Found: C, 64.60; H, 4.14; Cl, 12.00; N, 13.90%.

3-Phenyl-4-((pyridin-3-ylamino)methylene)-1*H*-pyrazol-5(4*H*)-one (8c)

It was obtained as pale yellow crystals from ethanol; m.p. 210-212 °C; yield 72%; IR (KBr) ν cm^{-1} 3200 (NH), 1638 (C=O); ^{1}H NMR (DMSO-d_6) δ = 7.21-7.80 (m, 11H, aromatic protons, alkenyl-H and NH), 9.77 (s, 1H, NH); MS: *m/z* (%) = 264 (M^+). *Anal.* Cacld for $C_{15}H_{12}N_4O$ (264.28): C, 68.17; H, 4.58; N, 21.20%. Found: C, 68.30; H, 4.60; N, 21.25%.

Preparation of 4-(aminomethylene)-3-phenyl-1*H*-pyrazole-5(4*H*)-one (10)

To a solution of the compound **5** (0.01 mole) in ethanol (20 mL), concentrated aqueous ammonia (0.7 mL) was added. The reaction mixture was refluxed for 6 h, and then cooled. The solid products so formed was filtered off, washed with dry ether, dried, it was obtained as bright red crystals from ethanol yield 76%; m.p. 270-272 °C; IR (KBr) ν cm^{-1} 3441, 3272 (NH_2), 1675 (C=O); ^{1}H NMR (DMSO-d_6) δ = 7.35-9.39 (m, 8H, aromatic protons, alkenyl proton and NH_2), 11.15 (s, 1H, NH); MS: *m/z* (%) = 187 (M^+). *Anal.* Cacld for $C_{10}H_9N_3O$ (187.20): C, 64.16; H, 4.85; N, 22.45%. Found: C, 64.25; H, 4.90; N, 22.53%.

Ethyl *N*-((5-oxo-3-phenyl-1*H*-pyrazol-4(5*H*)-ylidene)-methyl)formimidate (11)

A solution of compound **10** (0.01 mole) in a mixture of triethylorthoformate (0.01 mole) and acetic anhydride (2.5 mL) were heated under reflux for 3 hr during which the product partially separated. The reaction mixture was allowed to cool at room temperature and the separated product was filtered off, washed with ethanol, dried, and crystallized from the proper solvent to give **11**. It was obtained as pale yellow crystals from benzene; m.p. 238-239 °C; yield 78%; IR (KBr) ν cm^{-1} 3227 (NH), 2924 (CH-aliph), 1725 (C=O); ^{1}H NMR (DMSO-d_6) δ = 1.22 (t, 3H, CH_3), 3.61 (q, 2H, CH_2), 7.43-7.53 (m, 7H, aromatic and alkenyl protons), 12.84 (s, 1H, NH); MS: *m/z* (%) = 243 (M^+). *Anal.* Cacld for $C_{13}H_{13}N_3O_2$ (243.26): C, 64.19; H, 5.39; N, 17.27%. Found; C, 64.28; H, 5.45; N, 17.45%.

3-Phenylpyrazolo[4,3-*e*][1,3]oxazine (12)

A solution of compound **11** (0.01 mole) in pyridine (20 mL) was refluxed for 8 h. The solution was evaporated under vacuum and triturated with ethanol. The precipitated product was filtered off, washed with ethanol and crystallized from a mixture of EtOH/DMF (1:1) to give **12**. It was obtained as pale yellow crystals; m.p. 180-182 °C; yield 53%; IR (KBr) ν cm^{-1} 3050 (CH-arom); ^{1}H NMR (DMSO-d_6) δ = 7.46-9.76 (m, 7H, aromatic protons); ^{13}C NMR (DMSO-d_6) δ 123.45, 129.44, 130.90, 130.90, 131.95, 131.95, 133.87, 149.55, 153.00, 153.85, 171.00; MS: *m/z* (%) = 197 (M^+). *Anal*. Cacld for $C_{11}H_7N_3O$ (197.19): C, 67.00; H, 3.58; N, 21.31%. Found: C, 67.08; H, 3.65; N, 21.40%.

Preparation of compounds (15a,b)

General procedure

To a solution of compound **5** (0.01 mole) in ethanol

(20 mL), hydrazine hydrate (80%, 0.2 mL) or phenyl hydrazine (0.2 mL) was added. The reaction mixture was refluxed for 4 hrs, and then cooled. The solid product so formed was filtered off washed with ethanol, dried and crystallized from the proper solvent to give (**15a,b**).

4-(Hydrazinylmethylene)-3-phenyl-1*H*-pyrazol-5(4*H*)-one (15a)

It was obtained as yellow crystals from benzene; m.p. 110-112 °C; yield 49%; IR (KBr) ν cm^{-1} 3250, 3151 (NH), 1659 (C=O); ^{1}H NMR (DMSO-d_6) δ = 5.95 (s, 1H, alkenyl proton), 7.32-7.74 (m, 8H, aromatic protons, NH and NH_2), 8.53 (s, 1H, NH); MS: *m/z* (%) = 202 (M^+). *Anal.* Cacld for $C_{10}H_{10}N_4O$ (202.21): C, 59.40; H, 4.98; N, 27.71%. Found: C, 59.49; H, 5.10; N, 27.80%.

3-Phenyl-4-((2-phenylhydrazinyl)methylene)-1*H*-pyrazol-5(4*H*)-one (15b)

It was obtained as pale yellow crystals from benzene; m.p. 90-92 °C; yield 58%; IR (KBr) ν cm^{-1} 3205 (NH), 1660 (C=O); ^{1}H NMR (DMSO-d_6) δ = 6.65-7.96 (m, 13H, aromatic protons, alkenyl proton and 2NH), 9.87 (s, 1H, NH); MS: *m/z* (%) = 278 (M^+). *Anal.* Cacld for $C_{16}H_{14}N_4O$ (278.31): C, 69.05 ; H, 5.07; N, 20.13%. Found: C, 69.12; H, 5.17; N, 20.19%.

Preparation of compounds (16a,b)

General procedure

A solution of compound **15a** and **15b** (0.01 mole) in sodium ethoxide solution (prepared by dissolving 0.23 g of sodium in 20 mL absolute ethanol) was refluxed for 12 hr, and was allowed to cool to room temperature and diluted with ice-cold water (40 mL) containing few drops with HCl. The solid product so formed was filtered off washed with water, dried and crystallized from the proper solvent to give (**16a,b**).

4-Phenyl-1,2-dihydropyrazolo[3,4-*c*]pyrazole (16a)

It was obtained as green crystals from ethanol; m.p. 250-252 °C; yield 69%; IR (KBr) ν cm^{-1} 3214 (NH); ^{1}H NMR (DMSO-d_6) δ = 7.44-8.53 (m, 7H, aromatic protons and NH), 12.08 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 99.90, 127.90, 127.90, 128.55, 131.60, 131,60, 133.90, 134.90, 150.00, 169.90; MS: *m/z* (%) = 184 (M^+). *Anal.* Cacld for $C_{10}H_8N_4$ (184.20): C, 65.21; H, 4.38; N, 30.42%. Found: C, 65.33; H, 4.44; N, 30.50%.

2,4-Diphenyl-1,2-dihydropyrazolo[3,4-*c*]pyrazole(16b)

It was obtained as yellow crystals from ethanol; m.p. 207-209 °C; yield 59%; IR (KBr) ν cm^{-1} 3300 (NH), 3056 (CH-arom); ^{1}H NMR (DMSO-d_6) δ = 7.7-8.9 (m, 11H, aromatic protons and alkenyl proton), 11.90 (s, 1H, NH); MS: *m/z* (%) = 260 (M^+). *Anal.* Cacld for $C_{16}H_{12}N_4$ (260.29): C, 73.83; H, 4.65; N, 21.52%. Found: C, 73.90; H, 4.70; N, 21.59%.

Preparation of 4-phenyl-2*H*-pyrazolo[4,3-*d*]isoxazole (19)

A mixture of compound **5** (0.01 mole) and hydroxyl amine hydrochloride (0.01 mole) in 30 mL pyridine was refluxed for 12 hr. The solution was evaporated under vacuum and triturated with ice cold water (20 mL). The solid product so formed was collected by filtration, washed with water, dried, it was obtained as yellow crystals from ethanol yield 73%; m.p. 270-272 °C; IR (KBr) ν cm^{-1} 3214 (NH); 3066 (CH-arom); ^{1}H NMR (DMSO-d_6) δ = 7.35-8.75 (m, 7H, aromatic protons and NH); MS: *m/z* (%) = 185 (M^+). *Anal.* Cacld for $C_{10}H_7N_3O$ (185.18): C, 64.86; H, 3.81; N, 22.69%. Found: C, 64.90, H, 3.85, N, 22.74%.

Preparation of compounds (24a-c)

General procedure

A mixture of **3** (0.01 mole), and benzylidene malononitrile derivatives **20a-c** (0.01 mole) in ethanol (30 mL) was treated with a few drops of piperidine and heated under reflux for 4 hr. The reaction mixture allowed to cool, poured into crushed ice and acidified with HCl. The solid product was filtered off and crystallized from the proper solvent to give (**24a-c**).

6-Amino-3,4-diphenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (24a)

It was obtained as brown crystals from benzene; yield 81%; m.p. 200-202 °C; IR (KBr) ν cm^{-1} 3367, 3300 (NH_2) 3260 (NH), 2192 (C≡N); ^{1}H NMR (DMSO-d_6) δ = 5.22 (s, 1H, H-4 pyran), 7.01-7.64 (m, 12H, aromatic protons and NH_2), 11.82 (s, 1H, NH); MS: *m/z* (%) = 314 (M^+). *Anal.* Cacld for $C_{19}H_{14}N_4O$ (314.34): C, 72.60; H, 4.49; N, 17.82%. Found C, 72.69; H, 4.57; N, 17.90%.

6-Amino-4-(3-chlorophenyl)-3-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (24b)

It was obtained as brown crystals from benzene; yield 92%; m.p. 280-282 °C; IR (KBr) ν cm^{-1} 3300, 3250 (NH_2), 3061 (CH-arom), 2206 (C≡N), ^{1}H NMR (DMSO-d_6) δ = 5.07 (s, 1H, H-4 pyran), 6.99-7.47 (m, 11H, aromatic protons and NH_2), 12.18 (s, 1H, NH); MS: *m/z* (%) = 348 (M^+). *Anal.* Cacld for $C_{19}H_{13}ClN_4O$ (348.79): C, 65.43; H, 3.76; Cl, 10.16; N, 16.06%. Found: C, 65.50; H, 3.82; Cl, 10.00;

N, 16.10%.

6-Amino-4-(4-methoxyphenyl)-3-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (24c)

It was obtained as green crystals from ethanol; yield 88%; m.p. 276-278 °C; IR (KBr) ν cm^{-1} 3344, 3300 (NH_2), 2932 (CH-arom), 2215 (C≡N), ^{1}H NMR (DMSO-d_6) δ = 3.88 (s, 3H, OCH_3), 5.11 (s, 1H, H-4 pyran), 6.83-7.56 (m, 9H, aromatic protons), 8.65 (s, 2H, NH_2), 11.82 (s, 1H, NH); MS: *m/z* (%) = 344 (M^+). *Anal.* Cacld for $C_{20}H_{16}N_4O_2$ (344.37): C, 69.76; H, 4.68; N, 16.27%. Found; C, 69.80; H, 4.76; N, 16.32%.

Preparation of compounds (27a,b)

General procedure

A mixture of compound **3** (0.01 mole) and methyl carbonyl or benzoyl isothiocyanate (0.01 mole) in dry acetone (50 mL) was heated under reflux for 24 hr, then left to cool. The solid product that formed was filtered and crystallized from the proper solvent to give (**27a,b**).

***N*-(5-Oxo-3-phenyl-4,5-dihydro-1*H*-pyrazole-4-carbonothioyl)acetamide (27a)**

It was obtained as pale yellow crystals from benzene; yield 77%; m.p. 180-182 °C; IR (KBr) ν cm^{-1} 3328, 3266 (2 NH), 3054 (CH-arom), 2922 (CH-aliph), 1722, 1684 (2 C=O), 1580 (C=S); ^{1}H NMR (DMSO-d_6) δ = 2.2 (s, 3H, CH_3), 3.60 (s, 1H, CH), 6.90-8.90 (m, 5H, aromatic protons), 8.16 (s, 1H, NH), 13.16 (s, 1H, NH); MS: *m/z* (%) = 261 (M^+). *Anal.* Cacld for $C_{12}H_{11}N_3O_2S$ (261.30): C, 55.16; H, 4.24; N, 16.08; S, 12.27%. Found: C, 55.22; H, 4.30; N, 16.09; S, 12.21%.

***N*-(5-Oxo-3-phenyl-4,5-dihydro-1*H*-pyrazole-4-carbonothioyl)benzamide (27b)**

It was obtained as pale yellow crystals from benzene; yield 53%; m.p. 150-152 °C; IR (KBr) ν cm^{-1} 3306, 3152 (2 NH), 1744, 1682 (2C=O), 1585 (C=S); ^{1}H NMR (DMSO-d_6) δ = 3.33 (s, 1H, CH), 6.68-8.16 (m, 10H, aromatic protons), 8.16 (s, 1H, NH), 13.16 (s, 1H, NH); MS: *m/z* (%) = 323 (M^+). *Anal.* Cacld for $C_{17}H_{13}N_3O_2S$ (323.37): C, 63.14; H, 4.05; N, 12.99; S, 9.92%. Found; C, 63.20; H, 4.12; N, 13.10; S 9.95%.

Preparation of compounds (29a,b)

General procedure

A solution of compound **27a** or **27b** (0.01 mole) in sodium ethoxide solution (prepared by dissolving 0.23 g of sodium in 20 mL absolute ethanol) was refluxed for 8 hr, then left to cool at room temperature and poured in to ice/H_2O and acidified with HCl. The solid product so formed was collected by filtration, washed with water, dried, and crystallized from the proper solvent to give compound (**29a,b**).

6-Methyl-3-phenylpyrazolo[4,3-*e*][1,3]oxazine-4(1*H*)-thione (29a)

It was obtained as pale yellow crystals from benzene; yield 70%; m.p. 128-130 °C; IR (KBr) ν cm^{-1} 3190 (NH), 3054 (CH-arom), 2924 (CH-aliph); 1590 (C=S); ^{1}H NMR (DMSO-d_6) δ = 1.17 (s, 3H, CH_3), 7.10-7.61 (m, 5H, aromatic protons), 11.95 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 20.50, 110.40, 128.70, 129.10, 129.10, 129.25, 129.25, 134.00, 147.00. 147.90, 159.20, 205.50; MS: *m/z* (%) = 243 (M^+). *Anal.* Cacld for $C_{12}H_9N_3OS$ (243.28): C, 59.24; H, 3.73; N, 17.27; S, 13.18%. Found; C, 59.26; H, 3.75; N, 17.28; S, 13.20%.

3,6-Diphenylpyrazolo[4,3-*e*][1,3]oxazine-4(1*H*)-thione (29b)

It was obtained as brown crystals from ethanol; yield 64%; m.p. 120-122 °C; IR (KBr) ν cm^{-1} 3422 (NH), 3040 (CH-arom), 1585 (C=S); ^{1}H NMR (DMSO-d_6) δ = 6.98-7.92 (m, 10H, aromatic protons), 12.00 (s, 1H, NH); MS: *m/z* (%) = 305 (M^+) *Anal.* Cacld for $C_{17}H_{11}N_3OS$ (305.35): C, 66.87; H, 3.63; N, 13.76; S, 10.50%. Found: C, 66.93; H, 3.70; N, 13.80; S, 10.58%.

Preparation of compounds (32a-d)

General procedure

To a stirred cold solution of diazonium chloride (0.01 mole, prepared by treating of aniline derivatives (0.01 mole) with sodium nitrite (0.01 mole) in HCl, ethanol (30 mL) and catalytic of sodium acetate, the active methylene reagent **3** was added gradually. The stirring was continued for two hrs. The sold product so formed was filtered of, washed with water several times, dried and crystallized from the proper solvent to give (**32a-d**).

3-Phenyl-4-(2-phenylhydrazinylidene)-1*H*-pyrazol-5(4*H*)-one (32a)

It was obtained as pale red crystals from ethanol; yield 92%; m.p. 180-182 °C; IR (KBr) ν cm^{-1} 3435 (NH), 1636 (C=O); ^{1}H NMR (DMSO-d_6) δ = 7.19-8.08 (m, 11H, aromatic protons and NH), 12.11 (s, 1H, NH); MS: *m/z* (%) = 264 (M^+). *Anal.* Cacld for $C_{15}H_{12}N_4O$ (264.28): C, 68.17; H, 4.58; N, 21.20%. Found: C, 68.18; H, 4.59; N, 21.21%.

4-(2-(4-Methoxyphenyl)hydrazono)-3-phenyl-1*H*-pyrazol-5(4*H*)-one (32b)

It was obtained as brown crystals from ethanol; yield 88%; m.p. 212-214 °C; IR (KBr) ν cm^{-1} 3184 (NH), 1651 (C=O); ^{1}H NMR (DMSO-d_6) δ = 3.80 (s, 3H, OCH_3), 7.09-8.07 (m, 10H, aromatic protons and NH), 12.03 (s, 1H, NH); MS: *m/z* (%) = 294 (M^+). *Anal.* Cacld for $C_{16}H_{14}N_4O_2$ (294.31): C, 65.30; H, 4.79; N, 19.04%. Found: C, 65.39; H, 4.85; N, 19.10%.

4-(2-(3-Chlorophenyl)hydrazono)-3-phenyl-1*H*-pyrazol-5(4*H*)-one (32c)

It was obtained as orange crystals from ethanol; yield 91%; m.p. 250-252 °C; IR (KBr) ν cm^{-1} 3192 (NH), 3070 (CH-arom), 1659 (C=O); ^{1}H NMR (DMSO-d_6) δ = 7.44-8.05 (m, 10H, aromatic protons and NH), 12.05 (s, 1H, NH); MS: *m/z* (%) = 298 (M^+). *Anal.* Cacld for $C_{15}H_{11}ClN_4O$ (298.73): C, 60.31; H, 3.71; Cl, 11.87; N, 18.76. Found: C, 60.40; H, 3.79; Cl, 11.99; N, 18.82%.

4-(2-(4-Nitrophenyl)hydrazono)-3-phenyl-1*H*-pyrazol-5(4*H*)-one (32d)

It was obtained as pale red crystals from ethanol; yield 76%; m.p. 260-262 °C; IR (KBr) ν cm^{-1} 3209 (NH), 1671 (C=O); ^{1}H NMR (DMSO-d_6) δ = 7.46-8.31 (m, 9H, aromatic protons), 12.21 (s, 1H, NH), 13.60 (s, 1H, NH); MS: *m/z* (%) = 309 (M^+). *Anal.* Cacld for $C_{15}H_{11}N_5O_3$ (309.28): C, 58.25; H, 3.58; N, 22.64%. Found: C, 58.27; H, 3.60; N, 22.66%.

Preparation of compounds (35a-d)

General procedure

A mixture of **32a-d** (0.01 moles), active methylene reagent malononitrile (0.01 moles) and ammonium acetate (2.0 gm) was fused for 3.0 min in domestic microwave. The reaction mixture was left to stand, and then triturated with ethanol; the solid product so formed was collected by filtration and crystallized from the proper solvent to give **35a-d**.

6-Imino-3,5-diphenyl-5,6-dihydro-1*H*-pyrazolo[4,3-*c*]pyridazine-7-carbonitrile (35a)

It was obtained as brown crystals from ethanol; yield 58%; m.p. 180-182 °C; IR (KBr) ν cm^{-1} 3203 (NH), 2190 (C≡N); ^{1}H NMR (DMSO-d_6) δ = 7.23-8.06 (m, 11H, aromatic protons and NH), 12.09 (s, 1H, NH); MS: *m/z* (%) = 312 (M^+). *Anal.* Cacld for $C_{18}H_{12}N_6$ (312.33): C, 69.22; H, 3.87 N, 26.91%. Found: C, 69.23 H, 3.89 N, 26.93%.

6-Imino-5-(4-methoxyphenyl)-3-phenyl-5,6-dihydro-1*H*-pyrazolo[4,3-*c*]pyridazine-7-carbonitrile (35b)

It was obtained as orange crystals from ethanol; yield 67%; m.p. 170-172 °C; IR (KBr) ν cm^{-1} 3300 (NH), 2925 (CH-aliph), 2206 (C≡N); ^{1}H NMR (DMSO-d_6) δ = 3.78 (s, 3H, OCH_3), 7.05-8.06 (m, 10H, aromatic protons and NH), 12.01 (s, 1H, NH). MS: *m/z* (%) = 342 (M^+). *Anal.* Cacld for $C_{19}H_{14}N_6O$ (342.35): C, 66.66; H, 4.12; N, 24.55%. Found: C, 66.73; H, 4.20; N, 24.62%.

5-(3-Chlorophenyl)-6-imino-3-phenyl-5,6-dihydro-1*H*-pyrazolo[4,3-*c*]pyridazine-7-carbonitrile (35c)

It was obtained as red crystals from ethanol; yield 72%; m.p. 220-222 °C; IR (KBr) ν cm^{-1} 3191 (NH), 2187 (C≡N); ^{1}H NMR (DMSO-d_6) δ = 7.49-8.04 (m, 10H, aromatic protons and NH), 12.06 (s, 1H, NH). MS: *m/z* (%) = 346 (M^+). *Anal.* Cacld for $C_{18}H_{11}ClN_6$ (346.77): C, 62.34; H, 3.20; Cl, 10.22; N, 24.23%. Found: C, 62.42; H, 3.27; Cl, 10.25; N, 24.20%.

6-Imino-5-(4-nitrophenyl)-3-phenyl-5,6-dihydro-1*H*-pyrazolo[4,3-*c*]pyridazine-7-carbonitrile (35d)

It was obtained as brown crystals from ethanol; yield 81%; m.p. 240-242 °C; IR (KBr) ν cm^{-1} 3217 (NH), 2201 (C≡N); ^{1}H NMR (DMSO-d_6) δ = 7.50-8.27 (m, 10H, aromatic protons and NH), 12.20 (s, 1H, NH); MS: *m/z* (%) = 357 (M^+). *Anal.* Cacld for $C_{18}H_{11}N_7O_2$ (357.33): C, 60.50; H, 3.10; N, 27.44%. Found: C, 60.59; H, 3.17; N, 27.50%.

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