# Access to new Pyranopyrazoles and Related Heterocycles

A.K. Elziaty*, O. E.A. Mostafa, E.A. El-Bordany, M. Nabil and H.M.F. Madkour

*Synthetic Organic Chemistry Laboratory, Chemistry Department, Faculty of Science, Ain Shams University, Abbassia, Cairo, Egypt, post code 11566.*

*Tel.: 0224831836; fax: 0224831836*

**E-mail: ahm512@sci.asu.edu*.eg

Abstract— the hitherto unknown 6-amino-4-(4-chlorophenyl)-3-methyl-1, 4-dihydropyrano [2, 3-c] pyrazole-5-carbonitrile **3** was prepared and utilized as a synthon in annulation reactions to get new fused heterocycles. The structural features of these new compounds were confirmed by spectral analysis as well as elemental analyses.

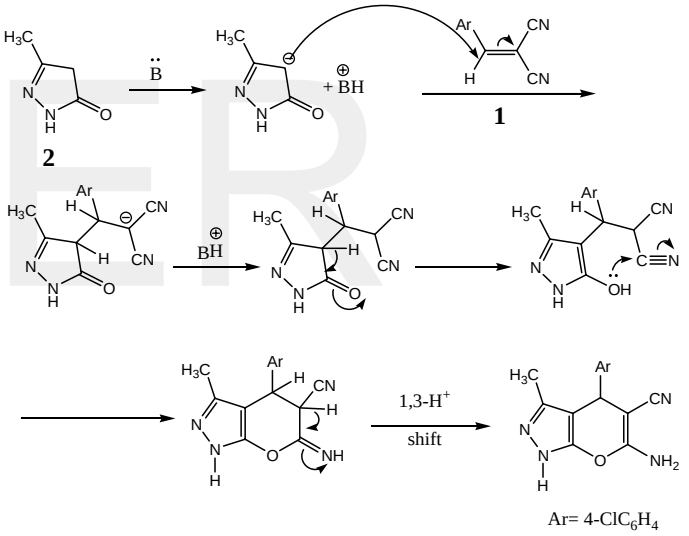
Index Terms— enaminonitrile, pyrazolopyranopyrimidine, pyranopyrazole, oxazinone, pyrimidinone, pyranopyrimidine and pyrimidinthione.

## 1. INTRODUCTION

It has been reported that pyran derivatives possess antitumor activity [1], hypotensive effect [2],plant growth regulation effects[3], anticancer activity[4],antifungal effect[5,6]. The literature survey also reveals that enaminonitrile derivatives were used in the synthesis of many biologically active heterocyclic compounds [7]. On the basis of these reports and as a further development to our previous work on the preparation of fused ring systems containing pyran moiety [8-12], we extended our investigation in synthesizing heterocyclic systems and evaluate their antimicrobial activity.

## 2. RESULTS AND DISCUSSION

In continuation of our program [8-12] on the synthesis of new heterocyclic systems from readily obtainable materials, herein, we report the synthesis of 6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano [2,3-c] pyrazole-5-carbonitrile 3 as starting material and study its behavior towards different reagents aiming to synthesize of some new heterocycles possessing antimicrobial activity. Thus the pyranopyrazole derivative 3 was prepared upon treatment of 2-(4-chlorobenzylidene)malononitrile1 with 3-methyl-1H-pyrazol-5(4H)-one 2 in the presence of few drops of piperidine. The formation of 3 was suggested to proceed via Michael's addition reaction followed by cyclization of the adduct, (Scheme 1). The structure of compound 3 was confirmed by spectral analysis (c.f. the experimental section).




Scheme 1

To study the behavior of 3 towards different electophilic reagents, compound 3 was allowed to react with acetic anhydride to afford the oxazinone derivative 4 as a result of acetylation of the amino group of 3 followed by cyclization and hydrolysis of the produced imino group to the carbonyl one. Strong evidence for the structure of 4 is the absorption band characteristic for lactone at 1737cm$^{-1}$ and the lack of any absorption bands for NH or $NH_2$ groups. The reaction of enaminonitrle with carbon disulfied is previously reported [13], the pyrazolopyranopyrimidine derivative 5 was prepared upon treatment of 3 with carbon disulfied in pyridine.

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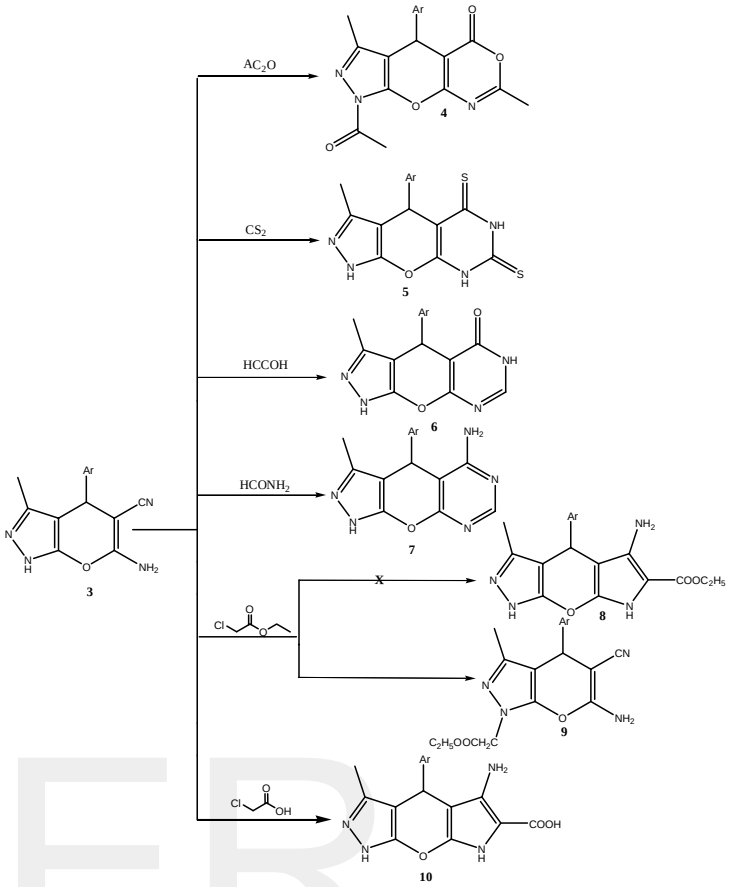
In accordance to the literature [13-18], the reaction of enaminonitrile3 with formic acid afforded the expected pyrimidinone derivative 6 which was idetified as 4-(4-chlorophenyl)-3-methyl-4,6 dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidin5 (1H)-one 6. The structure of 6 was confirmed by its spectral data and came in accordance with the previously reported [19,20]. Reaction of the enaminonitrile3 with formamide afforded the pyrimidine derivative 7whose structure was confirmed from its spectral data (cf. the experimental section). On studying the reaction of enaminonitile3 with ethyl chloroacetate, the expected product8is assumed to be formed via $SN^2$ mechanism of the amino group followed by cyclization on the cyano group. In our laboratory, it has been found that, treatment of 3 with ethyl chloroacetate afforded the unexpected product, ethyl 2-(6-amino-4-(4-chlorophenyl)-5-cyano-3-methylpyrano[2,3-c]pyrazol-1(4H)-yl)acetate 9 via $SN^2$ of the pyrazolo NH on the electrophilic carbon of ethyl chloroacetate (Scheme 2). Strong evidence for the structure of 9 is the lack of the signal of imino group NH of pyrazole moiety in $^1$HNMR, also the presence of absorption bands characteristic of the cyano group at 2192 $cm^{-1}$ and amino group at 3327 $cm^{-1}$and 3197 $cm^{-1}$ in IR spectrum of compound 9. (cf. experimental section). The pyrrolopyranopyrazole derivative 10 was obtained upon reaction of pyranopyrazole derivative 3 with chloroacetic acid (Scheme 2).




Scheme 2

The pyrazolopyranopyrimidine derivatives 11&12 were produced upon treatment of the pyranopyrazole3 with urea and / or thiourea respectively(Scheme 3). Benzoylation of the pyranopyrazole derivative 3 with benzoyl chloride afforded the oxazine derivative 13 whose structure was confirmed from the absence of a band characteristic of the cyano group in IR spectra as well as the presence of a band characteristic for the the carbonyl group at 1746 $cm^{-1}$. Also only one signal for labile NH in $^1$HNMR specrta. A chemical evidence of structure 3 is obtained from its condensation with p-chlorobenzaldehyde affording the schiff's base 14. When the enaminonitrile3 was allowed to react with the trimethylorthoformate it afforded the pyranopyrazole derivative 15 as a sole product. The structure 15 was confirmed by the presence of a characteristic band for the cyano group in IR spectrume at 2191 $cm^{-1}$ and the lack of a characteristic band for the amino group. The pyranopyrazole derivative 16 was obtained via the reaction of enaminonitrile derivative 3 with triethylorthoacetate. A chemical evidence for the structure of 16 is obtained from the formation of pyranopyrazolopyrimidine derivative 17 upon hydrazinolysis of compound 16. The hydrazine derivative 17 was allowed to react with carbon disulfied and/or acetic anhydride to afford the triazolthione derivative 18 and pyranopyrazolpyrimidene derivative 19 respectively(Scheme3).

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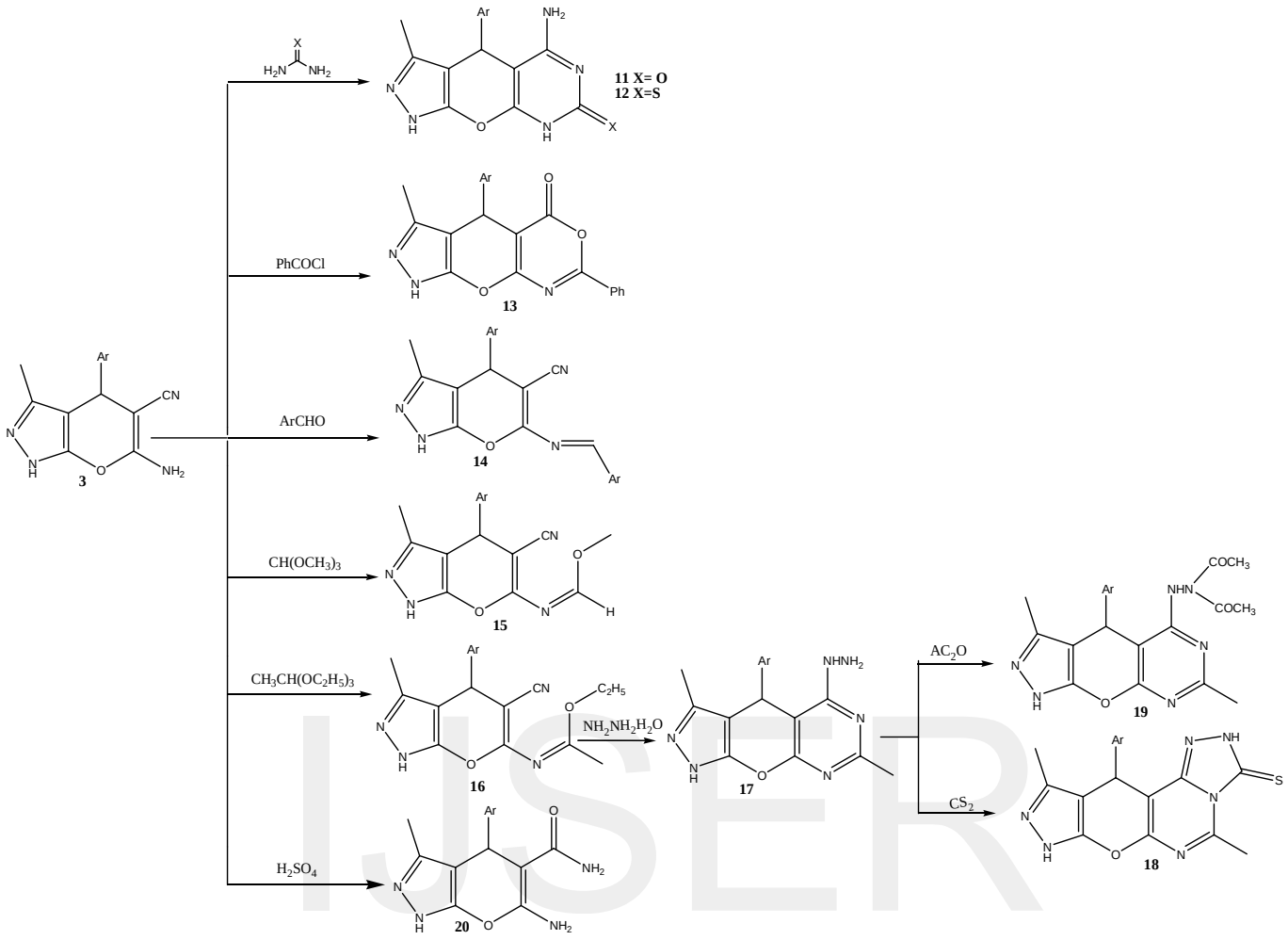


Scheme 3

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Partial hydrolysis of the enaminonitrle3 was carried out by treatment with sulfuric acid to afford the amide derivative 20 the structure of which was confirmed by the disappearance of a characteristic band for the cyano group in IR spectrum as well as appearance of a band characteristic of amide group at 1676 $cm^{-1}$. The structures of all the synthesized compounds were confirmed by their spectral data, the antimicrobial activity of some of selected compounds was also evaluated.

## 3. EXPERIMENTAL

All melting points were measured on a Gallenkamp electric melting point apparatus and are uncorrected. The infrared spectra were recorded in potassium bromide disks on a PyeUnicam SP-3-300 and Shimdazu FT IR 8101 PC Infrared spectrophotometers. The $^1$H-NMR was recorded on a Varian Mercury VX-300 NMR spectrometer. $^1$HNMR spectra were run at 300 MHz and on a Varian Gemini 200 MHz, Brucker AC-200 MHz using TMS as internal standard in deuterated chloroform ($CDC1_3$) or deuteratedimethylsulphoxide (DMSO-d6). Chemical shifts are quoted in $\delta$ and were related to that of the solvents. The mass spectra were recorded on a Shimadzu GCMS-QP-1OOOEX mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University. All the reactions and the purity of the new compounds were followed and cheeked by TLC.

*6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile 3:*

A solution of 2-(4-chlorobenzylidene)malononitrile 1 (1.88g, 10 mmole), 3-methyl- 1H-pyrazol-5(4H)-one 2 (0.98g, 0.01 mmole) and 0.2 mL of piperdine in ethanol (20 mL) was refluxed for an hour. The solid formed on hot was filtered off and crystallized from ethanol to give (3) as white crystals, m.p. 252-254ºC, yield 85%. Anal.Calcd.for $C_{14}H_{11}N_4ClO$ (286.72): C, 58.65; H, 3.87; N, 19.54. Found C, 58.53; H, 3.81; N, 19.49. IR ($\upsilon$/$cm^{-1}$): 3408,3307 ($NH_2$), 3232(NH), 2188(CN) and 1643 (bending $NH_2$). $^1$H-NMR (DMSO-d6) $\delta$ (ppm): 12.12 (s, 1H, NH,pyrazole, exchangeable with $D_2O$), 7.37 (2d, 4H,arom. J=8.7Hz), 6.90 (s, 2H, $NH_2$). 4.63(s, 1H, benzylic) and 1.79 (s 3H, $CH_3$) MS m/z (%): 286 (M.+; 14.8), 288 (7..3) ,175 (100) and 111 (5.0).

*1-acetyl-4-(4-chlorophenyl)-3,7-dimethyl-1,4-dihydro-5H-pyrazolo[4',3':5,6]pyrano[2,3-d][1,3]oxazin-5-one 4:*

A solution of 6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (3) (1.43g, 5 mmole) and acetic anhydride (20 mL) was refluxed on a hot plate for 8 hours, excess of acetic anhydride was removed using rotary evaporator. The solid remains after evaporation was crystallized from ethanol to give (4), as white crystals, m.p. 309-310ºC, yield 50%. Anal. Calcd. for $C_{18}H_{14}ClN_3O_4$ (370.80): C, 58.51; H, 3.80; N, 11.30. Found C, 58.13; H, 3.98; N, 15.09. IR ($\upsilon$/$cm^{-1}$): 1737,1656 (CO) and 1612(C=N). $^1$H-NMR (DMSO-d6) $\delta$ (ppm): 7.32-7.23 (m, 4H,arom.), 5.07(s, 1H, benzylic), 3.31 (s 3H, $CH_3$) and 2.29-2025 (m,6H,$2CH_3$), MS m/z (%): 371(M.+; 16.07), 372 (5.27), 328(6.06),330(2.58) 259(14.26) and 217 (100).

*4-(4-chlorophenyl)-3-methyl-4,8 dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine-5,7(1H,6H)-dithione 5:*

A mixture of 6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (3) (1.43g, 5 mmole) in dry pyridine (20 mL) and carbon disulphide (10 mL) was refluxed on a water bath for 24 hours, the excess solvent was removed under vacuum, the remained solid was collected and dissolved in hot dilute sodium hydroxide for 10 minutes, then the solution was filtered and acidified by acetic acid, the precipitated product was filtered off and washed with hot water, then crystallized from ethanol to give (5) as yellow crystals, m.p. 298-300ºC, yield 45%. Anal. Calcd. for $C_{15}H_{11}ClN_4OS_2$ (362.9): C, 49.65; H, 3.06; N, 15.44. Found C, 49.59; H, 2,96; N, 15.41. IR ($\upsilon$/$cm^{-1}$): 3399,3204 (NH) and 1091(C=S). $^1$H-NMR (DMSO-d6) $\delta$ (ppm): 11.25 (s,1H NH pyrazole, exchangeable with D2O), 8.64 (s,1H, NH, exchangeable with $D_2O$) 8.58 (s,1H, NH, exchangeable with ($D_2O$), 7.62 (d, 2H,arom.J=8.7), 7.37 (d, 2H,arom.J=8.4) 4.80 (s, 1H, benzylic), 2.02 (s 3H, $CH_3$). MS m/z (%): 363(M.+; 70.79), 348 (25.84), 283 (52.92), and 79 (100).

*4-(4-chlorophenyl)-3-methyl-4,6-dihydropyrazolo [4',3':5,6]pyrano[2,3-d]pyrimidin-5(1H)-one 6:*

A mixture of 6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (3) (1.43g, 5 mmole) and formic acid (20mL) was refluxed for 2 hours, The reaction mixture was poured after cooling into water and crushed ice, the solid formed was filtered off, washed with cold water and crystallized from ethanol to give (6) as color less crystals, m.p. 236-238ºC, yield 77%. Anal. Calcd. for $C_{15}H_{11}ClN_4O_2$ (314.7): C, 57.24; H, 3.52; N, 17.80. Found C, 57.25; H, 3.49; N, 17.76. IR ($\upsilon$/$cm^{-1}$): 3114, (NH) and 1696(CO).

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$^1$H-NMR (DMSO-d6) δ (ppm): 10.95 (s,2H NH pyrazole, and NH pyrimidinone, exchangeable with $D_2O$), 7.34-7.27 (m, 5H, 4H,arom. and N=CH), 4.13 (s, 1H, benzylic), 2.04 (s 3H, $CH_3$).

*4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrazolo [4',3':5,6]pyrano[2,3-d]pyrimidin-5-amine 7:*

A mixture of 6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (3) (1.43g, 5 mmole) and formamide (10mL) was refluxed with stirring at 100 $^o$C for 2 hours. The reaction mixture was poured after cooling into water and crushed ice; the solid formed was filtered off, washed with cold water and crystallized from dilute ethanol to give (7) as white crystals, m.p. 244-246ºC, yield 40%. Anal. Calcd. for $C_{15}H_{12}ClN_5O$ (313.79): C, 57.42; H,3.86; N, 22.32. Found C, 56.94; H, 3.79; N, 22.19. IR (υ/cm$^{-1}$): 3366,3203 (NH, $NH_2$) and 1624(bending$NH_2$). $^1$H-NMR (DMSO-d6) δ (ppm): 11.75 (s, 1H, NH,pyrazole, exchangeable with $D_2O$), 7.72 (s, 1H,N=CH), 7.65-7.3 (m, 4H,arom.) 7.10 (s, 2H $NH_2$ exchangeable with $D_2O$) 5.65 (s, 1H, benzylic), 2.10 (s 3H, $CH_3$). MS m/z (%): 313(M.+; 72.20), 296 (49.36), 270 (73), and 253 (100).

*Ethyl 2-(6-amino-4-(4-chlorophenyl)-5-cyano-3-methylpyrano[2,3-c]pyrazol-1(4H)-yl)acetate 9:*

A mixture of 6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (3) (1.43g, 5 mmole) and ethyl chloroacetate (0.61g, 5 mmole) in dry acetone (20mL) and potassium carbonate (1g) was refluxed for 12 hours, the excess acetone was distilled off under vacuum, the resulting mixture was poured into crushed ice and water with stirring. The resulting solid was filtered off and crystallized from dilute ethanol to give (9), as brown crystals, m.p. 171-173ºC, yield 40%. Anal. Calcd. for $C_{18}H_{17}ClN_4O_3$ (372.8): C, 57.99; H, 4.60; N, 15.03. Found C, 57.51; H, 4.57; N, 14.93. IR (υ/cm$^{-1}$): 3327,3197 ($NH_2$), 2192(CN) 1719 (CO) and 1631 (bending$NH_2$). 1H-NMR (DMSO-d6) δ (ppm): 8.24 (s,2H $NH_2$ exchangeable with $D_2O$), 7.77-7.61 (m, 4H, arom), 4.33-4.26 (q, 2H,$CH_2$), 3.82 (s,1H, benzylic), 2.50 (s, 3H $CH_3$) 3.33 (s, 2H $CH_2$) 1.23 (t, 3H,$CH_3$). MS m/z (%): 373(M.+; 25.48), 327 (5.34), 246 (100), 217 (10.28). and 173 (48.82).

*5-amino-4-(4-chlorophenyl)-3-methyl-4,7-dihydro-1H-pyrrolo[3',2':5,6]pyrano[2,3-c]pyrazole-6-carboxylic acid 10:*

A mixture of 6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (3) (1.43g, 5 mmole) and chloroacetic acid (0.47g, 5 mmole) in absolute ethanol (20ml) was refluxed for 12 hours, most of alcohol was removed under vacuum, the resulting mixture was poured into crushed ice and water with stirring. The solid formed was filtered off and crystallized from ethanol to give (10), as yellow crystals, m.p. 200-202ºC, yield 60%. Anal. Calcd. for $C_{16}H_{13}ClN_4O_3$ (344.75): C, 55.74; H, 3.80; N, 16.25. Found C, 55.34; H, 3.19; N, 15.99. IR (υ/cm$^{-1}$): 3480,3384 (brs. $NH_2$,NH,OH), 1707 (CO) $^1$H-NMR (DMSO-d6) δ (ppm): 11.10(s,1H NH pyrazole, exchangeable with $D_2O$),10.20 (s,1HCOOH exchangeable with $D_2O$), 7.65-7.49(m,4Harom.), 7.0(s,2H $NH_2$ exchangeable with $D_2O$), 6.97 (s, 1H, NH exchangeable with $D_2O$), 3.81 (s 4H, benzylic and $CH_3$). MS m/z (%): 345(45) 284(100) and 244(20)

*5-amino-4-(4-chlorophenyl)-3-methyl-4,8dihydropyrazolo[4/,3/:5,6]pyrano[2,3-d]pyrimidine-7(1H)-one 11*

A mixture of 6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (3) (1.43g, 0.005 mmole) and urea (0.3g, 05 mmole) in toluene was refluxed on a hot plate for 24 hours. The excess solvent was removed under vacuum; the solid remained was crystallized from dilute ethanol to give (11) as yellow crystals, m.p. 300-302ºC, yield 60%. Anal. Calcd. for $C_{15}H_{12}ClN_5O_2$ (329.76): C, 54.64; H, 3.67; N, 21.24;. Found C, 54.24; H, 3.47; N, 20.99. IR (υ/cm$^{-1}$): 3466(OH,NH), 3319,3150(NH,$NH_2$), 1614 (bending$NH_2$)and 1689(CO). $^1$H-NMR (DMSO-d6) δ (ppm): 12.41(s,1H NH pyrazole, exchangeable with $D_2O$),7,58(s,2H$NH_2$ exchangeable with $D_2O$), 7.35-7.24(m,4Harom.), 6.10(s,1H NH,OH exchangeable with $D_2O$), 4.68 (s, 1H, benzylic), 2.04 (s 3H, $CH_3$). MS m/z (%): 329(48.5), 299(18.7),214(100).

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*5-amino-4-(4-chlorophenyl)-3-methyl-4,8dihydropyrazolo[4/,3/:5,6]pyrano[2,3-d]pyrimidine-7(1H)-thioone 12*

A mixture of 6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile 3 (1.43g, 5 mmole) and thiourea (0.38g, 5 mmole) in toluene was refluxed on a hot plate for 24 hours. The excess solvent was removed under vacuum; the solid remained was crystallized from dilute ethanol to give (12) as yellow crystals, m.p. 224-227ºC, yield 80%. Anal.Calcd.for $C_{15}H_{12}ClN_5OS$ (345.82): C, 52.10; H, 3.50; Cl, 10.25; N, 20.25;. Found C, 51.91; H, 3.38; N, 19 .96. IR ($\upsilon$/cm$^{-1}$):330,13181 (NH,$NH_2$) and 1089(C=S), $^1$H-NMR (DMSO-d6) $\delta$ (ppm): 12.14(s,1H NH pyrazole, exchangeable with $D_2O$), 7.63-7.18 (m,4Harom.), 6,94 (s,2H$NH_2$ exchangeable with $D_2O$), 4.63 (s, 1H, benzylic), 3.72(s,1H SH, exchangeable with $D_2O$), 1.99 (s 3H, $CH_3$). MS m/z (%): 346(11), 312(8), 236(13), 57(100)

*4-(4-chlorophenyl)-3-methyl-7-phenyl-1,4-dihydro-5H pyrazolo[4',3':5,6]pyrano[2,3-d][1,3]oxazin-5-one 13:*

A mixture of 6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile 3 (1.43g 0.005 mmole) and benzoyl chloride (0.70g, 5 mmole) in toluene was refluxed for 24 hours. The excess solvent was removed under vacuum; the solid remained was crystallized from dilute ethanol to give (18) as yellow crystals, m.p. 144-146ºC, yield 60%. Anal.Calcd.for $C_{21}H_{14}ClN_3O_3$ (391.81): C, 46.37; H, 3.60; N, 10.72. Found C, 45.91.24; H, 3.47; N, 10 .46. IR ($\upsilon$/cm$^{-1}$): 3378(NH), 1746(CO). 1H-NMR (DMSO-d6) $\delta$ (ppm): 10.30 (s,1H NH pyrazole, exchangeable with $D_2O$), 7.80-7.22 (m,9Harom.), 4.73 (s, 1H, benzylic), 2.11 (s 3H, $CH_3$). MS m/z (%): 390(60) 347(29), 244(22) and 260(100)

*6-(4-chlorobenzylideneamino)-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile 14:*

A mixture of 6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile 3 (1.43g, 5 mmole) and 4-chlorobenzaldehyde (0.70g, 5 mmole) in toluene was refluxed for 24 hours. The excess solvent was removed under vacuum; the solid remained was crystallized from ethanol to give (14) as yellow crystals, m.p. 218-219ºC, yield 85%. Anal. Calcd. for $C_{21}H_{14}Cl_2N_4O$ (409.27): C, 61.63; H, 3.45; N, 13.69. Found C, 61.59.24; H, 3.39; N, 13 .46. IR ($\upsilon$/cm$^{-1}$): 3406 (NH), 2189(CN) and 1583 (C=N). 1H-NMR (DMSO-d6) $\delta$ (ppm): 9.58 (s,1H NH pyrazole, exchangeable with $D_2O$), 8.33(s, 1H N=CH), 7.70-7.02 (m,8Harom.), 4.37 (s, 1H, benzylic), 2.06 (s 3H, $CH_3$). MS m/z (%): 409(19), 383(25), 288(18) and 219(100)

*MethylN-4-(4-chlorophenyl)-5-cyano-3-methyl-1,4-dihydropyrano[2,3-c]pyrazol-6-ylformimidate (15)*

A mixture of 6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile 3 (1.43g, 5 mmole) and trimethylorthoformate (20mL) was refluxed for 24 hours. After reaction completion the excess orthoformate was removed under vacuum. The solid remained was washed with hexane several times, and crystallized from petroleum ether (80-100)- benzene to give (15) as yellow crystals, m.p. 180-183ºC, yield 80%. Anal. Calcd. for $C_{16}H_{13}ClN_4O_2$ (328.75): C, 58.45; H, 3.99; N, 17.04. Found C, 58.39.24; H, 3.86; N, 16 .91. IR ($\upsilon$/cm$^{-1}$): 3311(NH), 2191(CN) and 1643(C=N) $^1$H-NMR (DMSO-d6) $\delta$ (ppm): 12.11 (s,1H NH pyrazole, exchangeable with $D_2O$), 7.69(s, 1H N=CH), 7.43-7.18 (m,4Harom.), 4.63 (s, 1H, benzylic), 4.06 (s,3H $OCH_3$) 1.81 (s 3H, $CH_3$). MS m/z (%): 329(100), 221(32) and202 (38).

*Ethyl N-4-(4-chlorophenyl)-5-cyano-3-methyl-1,4-dihydropyrano[2,3-c]pyrazol-6-ylacetimidate (16):*

A mixture of 6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile 3 (1.43g, 5 mmole) and triethylorthoacetate (20mL) was refluxed for 24 hours. After reaction completion the excess ortho acetate was removed under vacuum to dryness. The solid remained was dissolved in minimum amount of ethanol, then poured into water with crushed ice, the solid formed was filtered off, washed with cold water and crystallized from dilute ethanol to give (16) as dark brown crystals, m.p. 130-132ºC, yield 75%.

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Anal.Calcd.for $C_{18}H_{17}ClN_4O_2$ (356.81): C, 60.59; H, 4.80; N, 15.70;. Found C, 60.39; H, 4.76; N, 14 .95. IR (υ/cm$^{-1}$): 3288 (NH), 2209(CN) and 1657(C=N). $^1$H-NMR (DMSO-d6) δ (ppm): 12.30 (s,1H NH pyrazole, exchangeable with $D_2O$), 7.48-7.27 (m,4Harom.), 4.90 (s, 1H, benzylic), 4.23 (q,2H $CH_2$, J=7.0Hz), 2.11 (s, 3H, $CH_3$), 1.81 (s, 3H, CH3), 1.28 (t, 3H, $CH_3$ J=7.0Hz). MS m/z (%): 356(17.69), 315(11.18), 287(100) and 221(73.34).

*4-(4-chlorophenyl)-5-hydrazino-3,7-dimethyl-1,4-dihydropyrazolo[4',3':5,6]pyrano [2,3-d]pyrimidine (17):*

A mixture Ethyl N-4-(4-chlorophenyl)-5-cyano-3-methyl-1,4-dihydropyrano[2,3-c]pyrazol-6-ylacetimidate 16 (1.78g, 5 mmole) and hydrazine hydrate (0.25g, 5 mmole) in (50ml) ethanol was refluxed for 12 hours. After reaction completion the excess ethanol was removed under vacuum to dryness. The solid remained was dissolved in minimum amount of ethanol, then poured into water with crushed ice, the solid formed was filtered off, washed with cold water and crystallized from dilute ethanol to give (17) as dark yellow crystals, m.p. 164-166ºC, yield 55%. Anal. Calcd. for $C_{16}H_{15}ClN_6O$ (342.78): C, 56.06; H, 4.41; N, 24.52;. Found C, 59.89; H, 4.39; N, 24 .45. IR (υ/cm-1): 3332(br. NH&$NH_2$) and 1626 (C=N), $^1$H-NMR (DMSO-d6) δ (ppm): 8.71 (s,1H NH pyrazole, exchangeable with $D_2O$), 7.91(s,2H $NH_2$ exchangeable with $D_2O$), 7.56(s,1H,NH exchangeable with $D_2O$), 7.48-7.25 (m,4Harom.), 4.80 (s, 1H, benzylic), 2.51 &2.08(2s, 6H,$CH_3$). MS m/z (%): 343(26.95), 231(23.36), 216(100) and 175(28.02).

*6-amino-5-carbamido-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole 18:*

A mixture of 4-(4-chlorophenyl)-5-hydrazino-3,7-dimethyl-1,4-dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine 17 (0.68g, 2 mmole) in dry pyridine (20 mL) and carbon disulphide (10 mL) was refluxed for 24 hours, the excess solvents was removed under vacuum, the remained solid collected and dissolved in hot dilute sodium hydroxide for 10 minutes, then the solution was filtered and the product precipitated on hot by acetic acid, the precipitated product was filtered off and washed with hot water, then crystallized from ethanol to give (18) as yellow crystals, m.p. 227-229ºC, yield 60%. Anal.Calcd.for $C_{17}H_{13}ClN_6OS$ (384.84): C, 53.06; H, 3.40; N, 21.84 Found C, 52.92; H, 3.39; N, 21 .65. IR (υ/cm$^{-1}$): 3215(br. NH), 1598 (C=N) and 1014(C=S). $^1$H-NMR (DMSO-d6) δ (ppm): 10.42 (s,1H NH pyrazole, exchangeable with $D_2O$), 7.13-752 (m,4Harom.), 5.21(s, 1H NH triazole exchangeable with $D_2O$), 4.45 (s, 1H, benzylic), 2.08 (s, 6H,$CH_3$). MS m/z (%): 384(17.83), 249(100), 204(19) and 154(12)

*3-[4-(4-chlorophenyl)-3,7-dimethyl-1,4-dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidin-5-yl]pentane-2,4-dione 19:*

A mixture of 4-(4-chlorophenyl)-5-hydrazino-3,7-dimethyl-1,4-dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine 17 (0.68g, 2 mmole) and acetic anhydride (10mL) was refluxed for 4 hours. After reaction completion the excess acetic anhydride was removed under vacuum to dryness. The solid remained was dissolved in minimum amount of ethanol, then poured into water with crushed ice, the solid formed was filtered off, washed with cold water and crystallized from dilute ethanol to give (19) as dark yellow crystals, m.p. 158-161ºC, yield 70%. Anal. Calcd. for $C_{20}H_{19}ClN_6O_3$ (426.86): C, 56.28; H, 4.49; N, 19.69 Found C, 56.12; H, 4.31; N, 19 .25. IR (υ/cm$^{-1}$): 3427(br. NH),1722(C=O) and 1600(C=N). $^1$H-NMR (DMSO-d6) δ (ppm): 12.03 (s,1H NH pyrazole, exchangeable with $D_2O$), 8.81(s, 1H NH exchangeable with $D_2O$), 6.69-6.76 (m,4Harom.), 4.49 (s, 1H, benzylic), 3.71(s,3H,$CH_3$), 3.31 (s, 6H,2$COCH_3$) and 1.82(s,3H,$CH_3$). MS m/z (%): 369(33)[M-(N$COCH_3$and $CH_3$)] 311(5) 315(6) 245(20) and 149(100)

*Pyrano[2,3-e]pyrazolo[5,6-e] 1,2,4triazolo[4,3-c]pyrimidine 20:*

6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile 3 (1.43g, 5 mmole) was added drop wise with stirring to conc. cold sulfuric acid at 20oC (6mL), the temperature does not exceed 40oC then the solution was stirred for further an hour at room temperature and poured onto an ice cold water (10mL). the reaction mixture was left overnight in the refrigerator. The white precipitate was filtered off and recrystallized from water to give (20) as colur

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less crystals.m.p 78-80oC. Anal. Calcd. for $C_{14}H_{13}ClN_4O_2$ (304.73): C, 55.18; H, 4.30; N, 18.39; Found C, 54.95; H, 4.25; N, 18 .25. IR ($\upsilon$/cm$^{-1}$): 3210(br. NH &$NH_2$), 1676(C=O) and 1599(C=N). $^1$H-NMR (DMSO-d6) $\delta$ (ppm): 11.01 (s,1H NH pyrazole, exchangeable with $D_2O$), 7.29-7.23(m, 4H $2NH_2$ exchangeable with $D_2O$), 7.15-7.06 (m,4Harom.), 4.16 (s, 1H, benzylic), and 1.89(s,3H,$CH_3$). MS m/z (%): 306(47), 290(61) 268(62) and 72(100)

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