HETEROCYCLIC SYNTHESIS WITH ACTIVATED NITRILES: AND EXPEDITUS SYNTHETIC APPROACH TO POLYFUNCTIONALLY SUBSTITUTED HETEROCYCLE PYRIMIDINES, PYRAZOLO, CHROMENO AND TETRAHYDROBENZO[B]THIOPHENE


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ABSTRACT

New derivatives of thioxo-7, 5-dihydro-H-pyrano [2,3-d] pyrimidine 3 was obtained from the reaction of compound 1a with acetic anhydride. Compound 1a was treated with acetic anhydride for 5 min and (or) acid chloride to yield the corresponding pyrano [2,3-d] pyrimidin-7-yl acetamide 5a and pyrano [2,3-d] pyrimidin-7-yl benzamide 5b derivatives. Treatment of compound 1a with bifunction compounds such as hydrazine hydrate, hydroxylamine hydrochloride, orthophenylene diamine, urea and ammonium thiocyanate to give compounds 6, 8, 10 and 12 respectively. Fusion of isolated compounds 6, 8, 10 and 12 in basic medium afforded the condensed pyrazolo, chromeno, pyrimido and thiopyrimidine 7, 9, 11 and 13 respectively. Treatment of compound 1b with ethylcyanoacetate afforded cyanoacetamide derivatives 15. The reactivity of compound 15 towards some electrophilic and nucleophilic reagents was also investigated. The structures of the products and conceivable mechanisms are discussed; the newly synthesized compounds were characterized by IR, 1H-NMR and mass spectral studies.

Key Words: Pyranopyridine, pyranopyrimidine and thioxopyrimidine

INTRODUCTION

Several derivatives of the pyrane or of fused pyrane ring systems are endowed with different types of biological activities. It has been reported that pyrane derivatives have attracted a great deal of interest owing to their antimicrobial activity (El-Agrody, et al, 2001; Bedair, et al, 2000; El-Agrody, et al, 2000), inhibition of influenza, virus sialidases (Taylor, et al, 1998), mutagenic activity (Hirmoto, et al, 1997), antiviral (Martnez and marco, 1997) and antiproliferation agents (Dell and smith, 1993), sex-pheromones (Bianchi and Tava, 1987), antitumor (Eiden and Denk, 1991) anti-inflammatory agents (Shishoo et al., 1981). Moreover pyrane derivatives are well known for antifungal and plant growth stimulating effects (Ohira and yatagai, 1993), central nervous system (CNS) activity (Eilden and Denk, 1991) and hypotensive effect (Tandom, et al, 1991).

In view of these observations and in continuation of our previous work in heterocyclic chemistry, we report here on the use of 7-amino-5-(4-chlorophenyl)-4-phenyl-2-thioxo-2, 5-dihydro-1H-pyra [2,3-d] pyrididine-6-carbonitrile 1a and 7-amino-4,5-diphenyl-2-thioxo-2,5-dihydro-1H-pyra [2,3-d] pyrididine-6-carbonitrile 1b as a key intermediate for the synthesis of new series of pyranopyrimidine, pyrano [2,3-d] pyrimidine benzamide, chromeno [2,3-e] diazpin derivatives, pyrano [2,3-d] pyrididine-7-yl-3-(dimethylamino) acrylamide and pyrano [2,3-d] pyridinin-7-yl-1H-pyrazole-4-carboxamide derivatives.

RESULTS AND DISCUSSIONS

This work is aimed to the synthesis of new compounds related to β-enaminonitriles of pyrano [2,3-d] pyrimidine derivatives. We have found...
that 1a is an attractive starting material for the preparation of some new fused heterocyclic compounds. Thus, it has been found that 1a reacted with acetic anhydride for a long time to give thioxo-2,5-dihydro-1H-pyran[2,3-d]pyrimidine 3 in a quantitative yield. The structure of 3 was based on its spectral analysis. The expected pyrimidine 2 formation was ruled out on the basis of analytical and spectral data (El-Gaby, et al, 2006) (Scheme 1).

Also, the acetamide derivatives 5a was achieved by the refluxing of compound 1a with acetic anhydride for 5 min. the structure of compound 5a was confirmed from its elemental and spectral analysis. Also, pyrano[2,3-d]pyrimidin-7-yl-acetamide 5a and pyrano[2,3-d]pyrimidin-7-yl-benzamide 5b were obtained by reaction of compound 1a with acid chloride derivatives in pyridine at reflux temperature [Siham, 2012; El-Sharkawy, et al, 2012; Fathy, et al, 2004]. Compound 1a was allowed to react with hydrazine hydrate in ethanol to give 6. Similar to this reaction, reaction of compound 1a with bifunction amino compounds such as orthophenylene diamine, urea and ammonium thiocyanate. Assignment of structure as 8, 10 and 12 were confirmed on the basis of their correct elemental analysis as well as compatible spectral data. While fusion of isolated intermediate 6, 8, 10 and 12 in ethanolic sodium ethoxide solution furnished the condensed pyrazolo, chromeno, pyrimido and thiopyrimidine 7, 9, 11, and 13 respectively. The 1H-NMR spectrum of compounds 7, 9, 11 and 13 are in agreement with proposed structures. Also, Compound 7 was obtained by reaction of 1a with hydroxylamine hydrochloride (El-Gaby, et al, 2006; Hatem, et al, 2005; Mohammed, et al; 1989; Sherif and Hussein, 1997; Ahmed, et al; Gamal, et al, 2005; Mohammed, et al; 2009, Said, et al, 2004) (scheme 2).

In continuation of our interest in developing the synthesis of polyfunctionally substituted heterooaromatics, we report here on the utility of 1b as a precursor for the synthesis of polyfunctionally substituted pyranopyrimidine, N-phenylacetohydrazonyl cyanide and cyclohexlideneacetamide derivatives. Some of the obtained products seem promising for further chemical transformations. Thus, a trial to prepare the 6-amino-7-cyano-4, 5-diphenyl-2-thioxo-5, 9-dihydro-2H-pyrimido [5',4':5,6] pyrano [2,3-d] pyrimidine-8-(1H)-one 14 through the interaction between 1b with ethylcyanoacetate in basic medium was unfortunately unsuccessful, but led interesting to compound 15 which formed as the reactants were mixed together in amount of sodium ethoxide. The actual structure of 15 was confirmed for the reaction product on the basis of their elemental and spectral data (Salman, 1999; Samir, et al, 2009; Haider, et al, 2012) (scheme 3).

The cyanoacetamide derivatives 15 react with dimethylformamidemethylacetal (DMF-DMA) to yield the corresponding enaminone 16 in high yield. The structure of the latter product was established on the basis of its elemental analysis and spectral data (Samir, et al, 2009; Haider, et al, 2012; Mohamed and Khaled, 2009). Compound 16 underwent an interamolecular heterocyclization upon boiling in hydrazine hydrate to afford aminopyrazole derivatives 17. The structure of compound 17 was confirmed for the reaction product on the basis of their elemental and spectral data Mohamed and [Haider, et al, 2012; Khaled, 2009]. In a similar manner, pyrano [2,3-d]pyrimidin-7-yl-1H-pyrazole-4-carboxamide derivatives 22 could be prepared by the reaction of enaminone 16 with malononitrile in refluxing ethanol.

The structure of 22 was based on its spectral analysis. Compound 22 was formed via Dimruth rearrangement (Haider, et al, 2012) illustrated in (scheme 4).

Furthermore, the behaviour of cyanoacetamide 15 towards some electrophilic reagent such as arylidenemalononitrile was also investigated. Thus, compound 15 was reacted with 4-chlorobenzylidenemalononitrile 23 in refluxing ethanol/Pip to give
Scheme 1

Scheme 2

Scheme 3
pyrimidinecarbonitrile derivatives 28. The coupling of 15 with arylidenediazonium chlorides gave the aryl hydrazones 30a-c (Haider, et al, 2012). On the other hand, the reaction of 15 with cyclohexanone in ethanol/Pip afforded a product 31. Compound 31 was confirmed by spectroscopic data and its chemical reactivity of this molecule to Gewald reaction with elemental sulfur. So, further reaction of compound 31 with elemental sulfur in refluxing DMF in the presence of little amount of piperidine afforded 32. Compound 32 was established by analytical spectra data and elemental analysis (Scheme 5).

**EXPERIMENTS**

All melting points were measured using Akofler Block instrument and are uncorrected. IR spectra (KBr) were recorded on a FTIR 5300 spectrometer ($\mu$, cm$^{-1}$). The $^1$H-NMR spectra were recorded in DMSO-d$_6$, CDCl$_3$ at 300 MHz on a Varian Gemini NMR. 1000 EX mass spectrometer at 70 ev. The purity of synthesized compounds was checked by thin layer chromatography TLC (aluminum sheets) using n-hexane, ethyl acetate (9:1, V/V, 7:3 V/V) eluent. Elemental analyses were carried out by
the Microanalytical Research Center, Faculty of Science, Cairo University.

**Procedure for the preparation of compound (3).** A mixture of 1a (3.92 g; 0.01 mol) and acetic anhydride (15 mL) was heated under reflux for 3 hrs. The reaction mixture was evaporated in vacuo and triturated with ethanol. The separated solid was filtered, washed with ether and crystallized from the proper solvent to give (3).

N-acetyl-N-(5-(4-chlorophenyl)-6-cyano-4-phenyl-2-thioxo-2,5-dihydro-1H-pyrano[2,3-d]pyrimidin-7-yl)acetamide (3). Formed as brown crystals from ethanol; yield (69%); M.p.112-114°C; IR (KBr) ν cm⁻¹ = 3215 (NH), 3064 (CH₇arom), 2934 (CH₇aliph), 2199 (CN), 1711 (CO) cm⁻¹; ¹H-NMR (DMSO-d₆) δ = 2.47 (s, 3H, CH₃), 2.48 (s, 3H, CH₃), 4.20 (s, 1H, 4H-pyrane), 7.20-7.71 (m, 9H, aromatic H), 10.20 (s, 1H, NH); MS: m/z (%) 476 (M⁺+2), Anal. Calcd. For C₂₄H₁₇ClN₄O₃S (474): C, 60.44; H, 3.59; N, 11.75; Found: C, 60.45; H, 3.61; N, 11.76 %.

**procedure for the preparation of compound (5a,b).** Method (A): A mixture of 1a (3.92 g; 0.01 mol) and acetic anhydride (15 mL) was heated under reflux for 5 Min. The reaction mixture was evaporated and allowed to cool. The separated solid was filtered, washed with water and crystallized from the proper solvent to give (5a).

Method (B): A mixture of 1a (3.92 g; 0.01 mol) and acetyl chloride 4a, benzoyl chloride 4b (0.01 mol) in pyridine (20 mL) was heated under reflux for 3 hrs. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered, washed with water and crystallized from the proper solvent to give (5a,b).

5-(4-chlorophenyl)-6-cyano-4-phenyl-2-thioxo-2, 5-dihydro-1H-pyrano [2,3-d]pyrimidin-7-yl)acetamide (5a). Formed as brown crystals from ethanol; yield (72%); M.p.180-182°C; IR (KBr) ν cm⁻¹ = 3454, 3234 (2NH), 3065 (CH-arom), 2924 (CH-aliph), 2190 (CN), 1710 (CO) cm⁻¹; ¹H-NMR (DMSO-d₆) δ = 1.91 (s, 3H, CH₃), 4.30 (s, 1H, 4H-pyrane), 7.30-8.60 (m, 11H, aromatic H and 2NH); MS: m/z (%) 436 (M⁺+2), Anal. Calcd. For C₂₂H₁₅ClN₄O₂S (434): C, 60.76; H, 3.48; N, 12.88; Found: C, 60.78; H, 3.89; N, 12.90 %.

N-(5-(4-chlorophenyl)-6-cyano-4-phenyl-2-thioxo-2,5-dihydro-1H-pyrano[2,3-d]pyrimidin-7-yl)benzamide (5b). Formed as brown crystals from ethanol; yield (74%); M.p.160-162°C; IR (KBr) ν cm⁻¹ = 3471 (NH), 3060 (CH₇arom), 2925 (CH-aliph), 2216 (CN), 1713 (CO) cm⁻¹; ¹H-NMR (CDCl₃) δ = 4.38 (s, 1H, 4H-pyrane), 7.26-8.10 (m, 16H, aromatic H and 2NH); MS: m/z (%) 498 (M⁺+2), Anal. Calcd. For C₂₇H₁₇ClN₄O₂S (496): C, 65.25; H, 3.45; N, 11.27; Found: C, 65.24; H, 3.43; N, 11.25%.

**procedure for the preparation of compound (6, 8, 10 and 12).** A mixture of 1a (3.92 g; 0.01 mol) and hydrazine hydrate, benzene-1,2-diamine, urea and ammonium thiocyanate (0.01 mol) respectively in ethanol (30 mL) containing catalytic amount of pyridine was heated under reflux for 12 hrs. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered, washed with water and crystallized from the proper solvent to give (6, 8, 10 and 12) respectively.

5-(4-chlorophenyl)-7-hydrazinyl-4-phenyl-2-thioxo-2,5-dihydro-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile (6). Formed as pale yellow crystals from ethanol; yield (83%); M.p.100-102°C; IR (KBr) ν cm⁻¹ = 3323, 3194 (NH₂), 2984 (CH-aliph), 2195 (CN) cm⁻¹; ¹H-NMR (DMSO-d₆) δ = 4.20 (s, 1H, 4H-pyrane), 5.20 (s, 2H, NH₂), 7.03-7.83 (m, 9H,
aromatic H), 8.67 (s, 1H, NH), 9.80 (s, 1H, NH); MS: m/z (%) 408 (M$^+$+1), Anal. Caled. For C$_{20}$H$_{14}$ClN$_5$O$_5$ (407.06): C, 58.89; H, 3.46; N, 17.17; Found: C, 58.90; H, 3.47; N, 17.19 %.

7-(2-aminophenylamino)-5-(4-chlorophenyl)-4-phenyl-2-thioxo-2,5-dihydro-1H-pyrazolo[2,3-d]pyrimidine-6-carbonitrile (8). Formed as pale yellow crystals from ethanol; yield (80%); M.p.140-142$^\circ$C; IR (KBr) ν cm$^{-1}$ = 2930 (CH-aliph), 2197 (CN) cm$^{-1}$; $^1$H-NMR (CDCl$_3$) δ = 4.12 (s, 1H, 4H-pyrane), 5.35 (s, 2H, NH$_2$), 7.10-7.80 (m, 14H, aromatic H and NH), 8.80 (s, 1H, NH); MS: m/z (%) 485 (M$^+$+2), Anal. Calcd. For C$_{26}$H$_{18}$ClN$_5$O$_5$ (483): C, 64.52; H, 3.75; N, 14.47; Found: C, 64.53; H, 3.77; N, 14.48 %.

5-(4-chlorophenyl)-6-cyano-4-phenyl-2-thioxo-2,5-dihydro-1H-pyrazolo[2,3-d]pyrimidine-7-yl carbamimide (10). Formed as orange crystals from ethanol; yield (80%); M.p.122-124$^\circ$C; IR (KBr) ν cm$^{-1}$ = 3446, 3351 (NH$_2$), 3214 (NH), 3065 (CH-arom) cm$^{-1}$; $^1$H-NMR (CDCl$_3$) δ = 4.14 (s, 1H, 4H-pyrane), 5.35 (s, 2H, NH$_2$), 7.11-7.72 (m, 9H, aromatic H and 2NH); MS: m/z (%) 435 (M$^+$), Anal. Calcd. For C$_{21}$H$_{14}$ClN$_5$O$_2$S (435): C, 57.86; H, 3.24; N, 16.07; Found: C, 57.87; H, 3.25; N, 16.08 %.

5-(4-chlorophenyl)-6-cyano-4-phenyl-2-thioxo-2, 5-dihydro-1H-pyrazolo[2,3-d]pyrimidin-7-yl carbamimidothioate (12). Formed as pale yellow crystals from ethanol; yield (86%); M.p.130-132$^\circ$C; IR (KBr) ν cm$^{-1}$ = 3455, 3400 (NH$_2$), 3056 (CH-arom) cm$^{-1}$; $^1$H-NMR (DMSO-d$_6$) δ = 4.80 (s, 1H, 4H-pyrane), 7.30-7.87 (m, 11H, aromatic H and NH$_2$), 10.00 (s, 1H, NH), 11.10 (s, 1H, NH); MS: m/z (%) 453 (M$^+$+2), Anal. Calcd. For C$_{21}$H$_{14}$ClN$_5$O$_2$S (451): C, 55.81; H, 3.12; N, 15.50; Found: C, 55.82; H, 3.13; N, 15.52 %.

procedure for the preparation of compound (7). Method (A): A solution of 6 in sodium ethoxide (30 mL) was heated under reflux for 12 hrs. The solution was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered, washed with water and crystallized from the proper solvent to give (7). Method (B): A mixture of 1a (3.92 g; 0.01 mol), hydroxyamine hydrochloride in glacial acetic acid (30 mL) containing anhydrous sodium acetate (1 g) was heated under reflux for 24 hrs. The reaction mixture was allowed to cool and poured into cold water (60 ml). The separated solid was filtered and crystallized to give (7).

4-(4-chlorophenyl)3-methyl-5-phenyl-4,8-dihydropyrazolo [4',3':5,6]pyrano[2,3-b]pyridine-7(2H)-thione (7). Formed as brown crystals from ethanol; yield (77%); M.p.126-128$^\circ$C; IR (KBr) ν cm$^{-1}$ = 3455, 3400 (NH$_2$), 3056 (CH-arom) cm$^{-1}$; $^1$H-NMR (DMSO-d$_6$) δ = 4.20 (s, 1H, 4H-pyrane), 5.20 (s, 2H, NH$_2$), 7.24-8.60 (m, 11H, aromatic H and 2NH); Anal. Calcd. For C$_{20}$H$_{14}$ClN$_5$O$_5$ (407): C, 58.89; H, 3.46; N, 17.17; Found: C, 58.90; H, 3.47; N, 17.19 %.

procedure for the preparation of compound (9, 11 and 13). A solution of 8, 10 and 12 in sodium ethoxide (30 mL) was heated under reflux for 12 hrs. The solution was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered, washed with water and crystallized from the proper solvent to give (9, 11 and 13).

13-(4-chlorophenyl)-1-phenyl-2-thioxo-pyrimidino[b]chromeno[2,3-e][1,4]diazpin-12-amine (9). Formed as brown crystals from ethanol; yield (79%); M.p.160-162$^\circ$C; IR (KBr) ν cm$^{-1}$ = 3384, 3102 (NH$_2$), 3061 (CH-arom), 2924 (CH-
aliph) cm$^{-1}$; $^1$H-NMR (CDCl$_3$) $\delta = 4.40$ (s, 1H, 4H-pyran), 5.40 (s, 2H, NH$_2$), 7.28-7.92 (m, 15H, aromatic H and 2NH); 4-amino-5-(4-chlorophenyl)-6-phenyl-8-thioxo-3,5,8,9-tetrahydro-2H-pyrimido[5',4':5,6]pyrano[2,3-d]pyrimidin-2-one (11). Formed as brown crystals from ethanol; yield (79%); M.p.164-166°C; IR (KBr) $\nu$ cm$^{-1}$ = 3452, 3400 (NH$_2$), 3060 (CH$_7$arom), 2924 (CH$_7$aliph), 1689 (CO) cm$^{-1}$; $^1$H-NMR (CDCl$_3$) $\delta = 4.14$ (s, 1H, 4H-pyran), 7.06-7.95 (m, 11H, aromatic H and 2NH); Anal. Calcd. For C$_{26}$H$_{18}$ClN$_5$O$_8$ (483): C, 64.52; H, 3.75; N, 14.47; Found: C, 64.53; H, 3.76; N, 14.48 %. 6-Damino-5-(4-chlorophenyl)-4-phenyl-5,7-dihydro-2H-pyrimido[5',4':5,6]pyrano[2,3-d]pyrimidine-2,8(1H)-dithione (13). Formed as pale yellow crystals from ethanol; yield (71%); M.p.150-152°C; IR (KBr) $\nu$ cm$^{-1}$ = 3440, 3400 (NH$_2$), 3061 (CH$_7$arom), 2920 (CH$_7$aliph), 1736 (CO) cm$^{-1}$; $^1$H-NMR (DMSO-d$_6$) $\delta = 4.20$ (s, 1H, 4H-pyran), 5.60 (s, 2H, NH$_2$), 7.45-7.80 (m, 11H, aromatic H and 2NH); Anal. Calcd. For C$_{21}$H$_{14}$ClN$_5$O$_2$S (451): C, 57.86; H, 3.24; N, 16.07; Found: C, 57.87; H, 3.26; N, 16.08 %. procedure for the preparation of compound (15). A mixture of 1b (3.58 g; 0.01 mol) and ethylcyanoacetate (0.01 mol) in sodium ethoxide (30 mL) was heated under reflux for 6 hrs. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered, washed with water and crystallized from ethanol to give (15). 2-cyano-N-(6-cyano-4,5-diphenyl-2-thioxo-2,5-dihydro-1H-pyran[2,3-d]pyrimidin-7-yl)acetamide (15). Formed as yellow crystals from ethanol; yield (88%); M.p.180-182°C; IR (KBr) $\nu$ cm$^{-1}$ = 3462, 3333 (2NH), 3059 (CH$_7$arom), 2926 (CH-aliph), 2215, 2189 (2CN), 1736 (CO) cm$^{-1}$; $^1$H-NMR (CDCl$_3$) $\delta = 3.72$ (s, 2H, CH$_3$), 3.80 (s, 1H, 4H-pyran), 7.06-7.95 (m, 11H, aromatic H and 2NH); Anal. Calcd. For C$_{26}$H$_{20}$N$_6$O$_2$S (480): C, 64.98; H, 4.20; N, 17.49; Found: C, 64.99; H, 4.21; N, 17.51 %. procedure for the preparation of compound (17). A mixture of 16 (4.80 g; 0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (50 mL) was heated under reflux for 8 hrs. The reaction mixture was left to stand and poured into water then acidified with HCl. The separated solid was filtered, washed with water and crystallized from the proper solvent to give (17). 5-amino-N-(6-cyano-4,5-diphenyl-2-thioxo-2, 5-dihydro-1H-pyran[2,3-d]
pyrimidin-7-yl)-1H-pyrazole-4-carboxamide (17). Formed as yellow crystals from ethanol; yield (71%); M.p. 150-152°C; IR (KBr) v cm⁻¹ = 3331, 3207 (NH₂), 3060 (CH-arom), 2923 (CH-ariph), 2208 (CN) cm⁻¹; ¹H-NMR (DMSO-d₆) δ = 4.20 (s, 1H, 4H-pyrane), 5.80 (s, 2H, NH₂), 7.21-7.80 (m, 14H, aromatic H, 3NH and CH-aroliffin); MS: m/z (%) 467 (M⁺), Anal. Calcd. For C₂₄H¹₇N₇O₂S (467): C, 61.66; H, 3.67; N, 20.97; Found: C, 61.67; H, 3.69; N, 20.98 %.

procedure for the preparation of compound (22). A mixture of 16 (4.80 g; 0.01 mol) and malononitrile (0.01 mol) in ethanol (30 mL) containing catalytic amount of piperidine was heated under reflux for 24 hrs. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered, washed with water and crystallized from the proper solvent to give (22).

5-Amino-N-(6-cyano-4,5-diphenyl-2-thioxo-2,5-dihydro-1H-pyran-2-yl)pyrimidin-7-yl)-1H-pyrazole-4-carboxamide (22). Formed as yellow crystals from ethanol; yield (74%); M.p. 150-152°C; IR (KBr) v cm⁻¹ = 3150 (NH), 2196 (CN), 1639 (CO) cm⁻¹; ¹H-NMR (CDCl₃) δ = 3.81 (s, 1H, 4H-pyrane), 7.23-7.95 (m, 14H, aromatic H and 3NH); MS: m/z (%) 503 (M⁺+2), Anal. Calcd. For C₃₃H₂₀ClN₇O₂S (613): C, 64.54; H, 3.28; N, 15.97; Found: C, 64.55; H, 3.29; N, 15.99 %.

procedure for the preparation of compound (30a-c). A cold suspension of aryl diazonium salts (0.002 mol) (prepared from 0.002 mol of aromatic amine with the appropriate quantities of sodium nitrite and hydrochloric acid) was gradually added to a cold solution (0-5°C) of 15 (0.002 mol) in ethanol (50 mL) containing anhydrous sodium acetate (5 g) with continuous stirring for 1 hr. The resulting reaction product was filtered off, washed with water and crystallized from the proper solvent to give compounds (30a-c).

2-(6-cyano-4,5-diphenyl-2-thioxo-2,5-dihydro-1H-pyran-2-yl)pyrimidin-7-ylamino)-2-oxo-N'(4-chlorophenyl)acetohydrazonoyl cyanide (30a). Formed as orange crystals from ethanol; yield (86%); M.p.110-112°C; IR (KBr) v cm⁻¹ = 3439, 3384 (2NH), 2961 (CH-arom), 2930 (CH-ariph), 2210 (CN), 1631 (CO) cm⁻¹; ¹H-NMR (CDCl₃) δ = 4.40 (s, 1H, 4H-pyrane), 7.02-7.94 (m, 17H, aromatic H and 3NH); MS: m/z (%) 529 (M⁺), Anal. Calcd. For C₂₉H₁₉N₇O₂S (529): C, 65.77; H, 3.62; N, 18.51; Found: C, 65.78; H, 3.63; N, 18.52.

N'(4-chlorophenyl)-2-(6-cyano-4,5-diphenyl-2-thioxo-2,5-dihydro-1H-pyran-2-yl)pyrimidin-7-ylamino)-2-oxoacetoyl...
hydrazonoyl cyanide (30b). Formed as orange crystals from ethanol; yield (83%); M.p.114-116°C; IR (KBr) ν cm⁻¹ = 3442, 3181 (2NH), 3063 (CH-aram), 2925 (CH-aliph), 2212 (CN), 1639 (CO) cm⁻¹; ¹H-NMR (DMSO-d₆) δ = 4.20 (s,1H, 4H-pyrane), 7.23-8.20 (m, 17H, aromatic H and 3NH); MS: m/z (%) 563 (M⁺), Anal. Calcd. For C₂₉H₁₈ClN₇O₂S (563): C, 61.76; H, 3.22; N, 17.38; Found: C, 61.77; H, 3.23; N, 17.40 %.

2-(6-cyano-4,5-diphenyl-2-thioxo-2,5-dihydro-1H-pyran-2,3-dipyrimidin-7-ylamino)-2-oxo-N'-p-tolylacetohydrazonoyl cyanide (30c). Formed as orange crystals from ethanol; yield (80%); M.p.122-124°C; IR (KBr) ν cm⁻¹ = 3452, 3378 (2NH), 3062 (CH-aram), 2931 (CH-aliph), 2212 (CN), 1629 (CO) cm⁻¹; ¹H-NMR (CDCl₃) δ = 2.09 (s,3H, CH₃), 4.30 (s,1H, 4H-pyrane), 7.08-8.00 (m, 17H, aromatic H and 3NH); MS: m/z (%) 543 (M⁺), Anal. Calcd. For C₃₀H₂₁N₇O₂S (543): C, 66.28; H, 3.89; N, 18.04; Found: C, 66.29; H, 3.90; N, 18.05 %.

procedure for the preparation of compound (31). A mixture of dihydropyrimidinone derivatives 15 (4.25 g; 0.01 mol) and cyclohexanone (0.01 mol) in ethanol (50 mL) containing catalytic amount of piperidine was heated under reflux for 6 hrs. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered, washed with water to give (31).

2-cyano-N-(6-cyano-4,5-diphenyl-2-thioxo-2,5-dihydro-1H-pyran-2,3-dipyrimidin-7-yl)-2-cyclohexideneacetamide (31). Formed as yellow crystals from ethanol; yield (82%); M.p.122-124°C; IR (KBr) ν cm⁻¹ = 3328, 3203 (2NH), 3060 (CH-aram), 2923 (CH-aliph), 2204 (CN), 1626 (CO) cm⁻¹; ¹H-NMR (CDCl₃) δ = 0.87-1.71 (m, 6H, 3CH₂), 3.14-3.97 (m, 4H, 2CH₂), 4.50 (s, 1H, 4H-pyrane), 7.27-7.98 (m, 12H, aromatic H and 2NH); MS: m/z (%) 537 (M⁺), Anal. Calcd. For C₃₀H₂₃N₇O₂S (537): C, 64.78; H, 4.31; N, 13.03; Found: C, 64.79; H, 4.30; N, 13.04 %.

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الكلمات الإرشادية: بيرازولوربين، بيرازولوربين وثيوسبيرينات.

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