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ABSTRACT

A series of new thioxopyrimidine, 4H-pyrans, pyranopyridine and pyranopyrimidine derivatives with expected biological activity have been prepared through the reaction of 6-phenyl-2-thioxo-2,3-dihydropyrimidin-4(5H)-one 4 and 7-Amino-5-(4-chlorophenyl)-4-phenyl-2-thioxo-2,5-dihydro-1H-pyran[2,3-d]pyrimidine-6-carbonitrile 11b with some electrophilic reagents and nucleophilic reagents. The newly synthesized compounds were characterized by IR, 1H-NMR and mass spectral studies.

Key Words: Thioxopyrimidine, 4H-pyran, pyranopyridine and pyranopyrimidine

INTRODUCTION

Thioxopyrimidine is an essential structural unit of several heterocycles, which display a wide range of interesting biological and pharmacological properties such as anticancer and antimicrobial activities (Cocco et al., 2001).

Also, pyrimidinethiones have been found to possess antitubercular (Paghdar et al., 2007), antitumor (Ozaki et al., 1984) and hypoglycemic activities (Baucer and Safir, 1968).

On the other hand, 4H-pyran and their derivatives are of considerable interest due to their pharmacological activities (Green et al., 1995), such as spasmylocytic, diuretic, anticoagulant, anticancer, and antianaphylactic activity (Abdelrazek et al., 2007; Bonsignore et al., 1993; Witte et al., 1986). In addition, 4H-pyran are useful intermediates for synthesis of various compounds, such as pyranopyridine derivatives (Lei and Hu, 2011) and pyranopyrimidines (Quintela et al., 1995).

RESULTS AND DISCUSSIONS

Pyrimidinethione 4 was prepared through the two-component reaction of thiourea and ethylbenzoylacetaate. The structure of the reaction product could be

Also, various pyranopyrimidinethiones exhibit antimicrobial (Eid et al., 2004), antibacterial (Abd El-Wahhab, 2002), antigenotoxic (Chabchoub et al., 2007) and antifungal activities (Bedar et al., 2000; Bedar et al., 2000; Khafagy et al., 2002).

Moreover, pyranopyrimidines derivatives can have antiplatelet, antithrombotic (Bruno et al., 2006), analgesic, anti-inflammatory, and antiphlogist activity (Bruno et al., 2004; Bruno et al., 2002).

In view of these observations and in continuation of our previous work in heterocyclic chemistry, we synthesized some new pyranopyrimidinethione and chromenopyrimidinethione derivatives using 6-phenyl-2-thioxo-2,3-dihydropyrimidin-4(5H)-one as starting materials aiming to develop a new synthetic route for synthesing new heterocyclic derivatives.
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The active methylene group in 2-thioxo-2,3-dihydropyrimidine derivatives 4 was exploited to synthesize novel pyranopyrimidine, chromenopyrimidinethione and pyrido[3',2':5,6]pyrano[2,3-b]pyridine derivatives through its reactions with some electrophile reagents.

Thus, Compounds 11a-e were synthesized in quantitative yield, when 4 is allowed to react with arylidenemalononitrile derivatives 6a-e under reflux in ethanol and in the presence of catalytic amounts of piperidine.

The structure of compound 11a was established based on analytical and spectral data [Mahmoud et al, 2012; Saied et al; Hala and Mona, 2012]. In a similar manner, the reaction of 4 with α, β-unsaturated ketones 12a-e in the presence of piperidine led to the formation of pyranopyrimidinethione derivatives 16a-e [El-Saied et al, 2004] (Scheme 2). A mixture of formaldehyde and malononitrile was reacted with compound 4 in refluxing ethanol/piperidine to give 20 [Elagamy et al, 2006; El-Gaby et al, 2006]. Pyranopyrimidine carbonitrile derivatives 24a-b was synthesized by cyclocondensation of compound 4 with ethoxymethyleneamalonitrile, ethyl-2-cyano-3-ethoxyacrylate 21a,b in refluxing ethanol and catalytic amounts of piperidine.

The structure of 24a was established on the basis of its elemental analysis and spectral data. Compound 24b is assumed to be formed via intermediate formation followed by elimination of ethanol.

In a similar manner, cyclization of benzylidene cyclohexanone derivatives 25a-d with dihydropyrimidinone derivatives 4 in ethanol at reflux temperature in the presence of piperidine produced the chromenopyrimidinethione derivatives 29a-d [El-Gaby et al, 2006], all the analytical and spectral data of compounds 29a-d are in agreement with the proposed structures.

The formation of 29a-d were proposed to proceed via the Michael type addition of the active methylene group in dihydropyrimidinone derivatives 4 to the activated double bond in 25a-d to give Michael adducts which readily cyclized to yield 29a-d via losing water molecule (Scheme 3). In continuation of our previous interest in the synthesis of variety of heterocycles from readily obtainable inexpensive starting materials we report here on the utility of 7-amino-5-(4-chlorophenyl)-2-thioxo-2,5-dihydro-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile 11b for the synthesis of some novel heterocycles incorporating pyrimidinethione moiety. So, when compound 11b allowed to react with chloroacetyl chloride 30 in refluxing dioxane it afforded the novel 2-chloroacetimidate derivatives 31 in acceptable yield (80%).
The structure of compound 31 was established on the basis of analytical and spectral data. Furthermore the reaction of 11b with chloroacetyl chloride 30 in dioxane under reflux for 24 hrs gave pyrano[2,3-d:6,5-d']dipyrimidin-6(2H)-one derivatives 32. Compound 32 was obtained by fusion of compound 31 over melting point without solvent in presence of ammonium acetate [Mansour et al, 2011; Afaf et al 2013].

Compound 11b was reacted with benzylidenemalononitrile 6a in ethanol in the presence of a catalytic amount of piperidine under reflux to give the corresponding pyrido[3',2':5,6] pyrano[2,3-d] pyrimidine[7] carbonitrile 33. The IR, 1H-NMR and mass spectra of compound 33 is in agreement with the proposed structure (El-Gaby et al., 2006) (scheme 4) Compound 11b condensed with dimethylformamididedimethylacetal (DMF-DMA) to yield 34. The Pyrimidinethiones derivatives 35 was obtained by the reaction of compound 11b with formamide. Compound 34 could be readily converted in to pyrano[2,3-d]pyrimidine 35 on treatment with AcOH in the presence of ammonium acetate mixture. Structure of compound 35 was established through spectral analysis (Said et al., 2007; Gamal et al., 2005; Nada et al.; 2008) (Scheme 4).

**EXPERIMENTS**

Melting points were determined using a Büchi apparatus and are uncorrected. The purity of compound was confirmed by TLC using Merck silica gel 60F254 plates using toluene, ethyl acetate and methanol as a mobile phase and spots were visualized under UV radiation. IR spectra (KBr) were recorded on a Bruker-Vector 22 instrument (Bruker) and frequencies are expressed in cm\(^{-1}\). \(^1\)H NMR spectra were recorded with a Varian Gemini spectrometer (300 MHz and 200 MHz) with TMS as the internal reference. Chemical shifts were reported on appm scale (\(\delta\)) relative to TMS as a standard.

The mass spectra were recorded with a HP D5988 A 1000 MHz instrument (Hewlett-Packard). Elemental analyses were performed at the Microanalytical Centre at the Faculty of Science, Cairo University, Egypt.

**procedure for the preparation of compounds (4,5).**

A mixture of thiourea (0.76 g, 0.01 mol) and ethyl benzoyleacetate (1.92 g, 0.01 mol) was stirred overnight without solvent for 24 hrs at room temperature. The solid product formed was filtered off, washed with diethyl ether and crystallized from ethanol to give (4, 5).
Scheme 3

Scheme 4

Scheme 4
6-phenyl-2-thioxo-2,3-dihydropyrimidin-4(5H)-one (4). It was obtained as white crystals yield (83%); m.p.145—147°C; 1H—NMR (DMSO—d6) δ: 4.17 (s, 2H, CH2), 7.02—7.57 (m, 6H, aromatic H and NH); IR (KBr) ν cm−1: 3380 (NH), 3175 (CH—arom), 1618 (C=O) cm−1; MS: m/z (%) 205 (M+1), Anal. calcd for C10H6N2O3S: C, 58.80; H, 3.34; N, 14.27; Cl, 9.01; S, 8.15%.

7-hydroxy-4-phenylpyrimidine-2(1H)-thione (5).

It was obtained as yellow crystals yield (5%); m.p.240—242°C; 1H—NMR (DMSO—d6) δ: 6.07 (s, 1H, CH—oliffin), 7.48—7.70 (m, 6H, aromatic H and NH), 12.49 (s, 1H, OH); IR (KBr) ν cm−1: 3400 (OH), 3159 (NH) cm−1; MS: m/z (%) 205 (M+1), Anal. calcd for C10H8N2O3S (204): C, 58.80; H, 3.95; N, 13.72; S, 15.70; Found: C, 58.82; H, 3.97; N, 13.73; S, 15.69%.

procedure for the preparation of pyranopyrimidine derivatives (11a—e).

A mixture of dihydropyrimidinone derivatives (4) (2.04 g; 0.01 mol) and arylidenemalononitriles (6a—e) (0.01 mol) in ethanol (50 mL) containing catalytic amount of pipridine 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 off, washed with water and crystallized to give (11a—e).

7-Amino-4,5-diphenyl-2-thioxo-2,5-dihydropyrimidine-6-carbonitrile (11a).

Formed as white crystals from ethanol; yield (82%); m.p.108—110°C; 1H—NMR (DMSO—d6) δ: 4.97 (s, 1H, 4H—pyrane), 6.13 (s, 2H, NH2); 9.73 (s, 1H, NH), 7.05—7.79 (m, 10H, aromatic H); IR (KBr) ν cm−1: 3329, 3203 (NH), 3050 (CH—arom), 2934 (CH—aliph), 2185 (CN) cm−1; MS: m/z (%): 359 (M+1), Anal. calcd for C20H14N3O3S (388): C, 67.02; H, 3.94; N, 15.63; S, 8.95; Found: C, 67.02; H, 3.95; N, 15.65, S, 8.93%.

7-Amino-5-(4-chlorophenyl)-4-phenyl-2-thioxo-2,5-dihydro-1H-pyran[2,3-d]pyrimidine-6-carbonitrile (11b).

Formed as yellow crystals from ethanol; yield (84%); m.p.186—188°C; 1H—NMR (DMSO—d6) δ: 5.02 (s, 1H, 4H—pyrane), 6.15 (s, 2H, NH2), 7.00—7.84 (m, 10H, aromatic H and NH); IR (KBr) ν cm−1: 3471, 3332 (NH2), 2924 (CH—aliph), 2218 (CN) cm−1; MS: m/z (%) 392 (M+), Anal. calcd for C20H13ClN3O3S (392): C, 61.14; H, 3.34; N, 14.26; Cl, 9.02; S, 8.16; Found: C, 61.15; H, 3.36; N, 14.27; Cl, 9.01; S, 8.15%.

7-Amino-5-(2-nitrophenyl)-4-phenyl-2-thioxo-2,5-dihydro-1H-pyran[2,3-d]pyrimidine-6-carbonitrile (11c).

Formed as pale yellow crystals from ethanol; yield (78%); m.p.150—152°C; 1H—NMR (CDCl3) δ: 4.38 (s, 1H, 4H—pyrane), 6.62 (s, 2H, NH2), 6.95—8.54 (m, 9H, aromatic H), 9.28 (s, 1H, NH); IR (KBr) ν cm−1: 3336, 3200 (NH2), 2936 (CH—aliph), 2191 (CN) cm−1; MS: m/z (%) 403 (M+), Anal. calcd for C20H13N3O3S (403): C, 59.55; H, 3.25; N, 17.36; S, 7.95; Found: C, 59.56; H, 3.27; N, 17.37; S, 7.94%.

7-Amino-5-(4-methoxyphenyl)-4-phenyl-2-thioxo-2,5-dihydro-1H-pyran[2,3-d]pyrimidine-6-carbonitrile (11d).

Formed as green crystals from ethanol; yield (70%); m.p.180—182°C; 1H—NMR (DMSO—d6) δ: 3.71 (s, 3H, OCH3), 3.84 (s, 1H, 4H—pyrane), 7.02—7.85 (m, 12H, aromatic H+NH2); IR (KBr) ν cm−1: 3401, 3214 (NH2), 2933 (CH—aliph), 2197 (CN) cm−1; MS: m/z (%) 388 (M+), Anal. calcd for C21H14N3O3S (388): C, 64.93; H, 4.15; N, 14.42; S, 8.25; Found: C, 64.94; H, 4.16; N, 14.44; S, 8.23%.
7-Amino-5-methyl-4-phenyl-2-thioxo-2,5-dihydro-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile (11e).

Formed as pale green crystals from ethanol; yield (78%); m.p. 170—172 °C; \(^1\)H—NMR (DMSO—d\(_6\)) \(\delta\): 2.27 (s, 3H, CH\(_3\)), 4.09 (s, 1H, 4H—pyrane), 6.22 (s, 2H, NH\(_2\)), 6.39—8.04 (m, 6H, aromatic H and NH); IR (KBr) \(\nu\) cm\(^{-1}\): 3349, 3228 (NH\(_2\)), 2932 (CH—aliph), 2193 (CN) cm\(^{-1}\); MS: \(m/z\) (%): 296 (M\(^+\)), Anal. calcd for C\(_{15}\)H\(_{12}\)N\(_4\)OS (296): C, 60.79; H, 4.08; N, 18.91; S, 10.82; Found: C, 60.80; H, 4.09; N, 18.93; S, 10.81 %.

procedure for the preparation of pyranopyrimidinethione derivatives (16a—c).

A mixture of dihydropyrimidinone derivatives (4) (2.04 g; 0.01 mol) and chalcones (12a—c) (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 off, washed with water and crystallized from the proper solvent to give (16a—c).

4,5,7-triphenyl-1H-pyra[2,3-d]pyrimidine-2(5H)-thione (16a).

Formed as pale yellow crystals from ethanol; yield (88%); m.p. 100—102 °C; \(^1\)H—NMR (DMSO—d\(_6\)) \(\delta\): 5.10—5.11 (d, 1H, CH—oliffin), 5.38—5.40 (d, 1H, 4H—pyrane), 6.78—8.53 (m, 15H, aromatic H), 9.88 (s, 1H, NH); IR (KBr) \(\nu\) cm\(^{-1}\): 3181 (NH), 3083 (CH—arom), 2962 (CH—aliph) cm\(^{-1}\); MS: \(m/z\) (%): 394 (M\(^+\)), Anal. calcd for C\(_{25}\)H\(_{18}\)N\(_2\)OS (394): C, 76.12; H, 4.60; N, 7.10; S, 8.13; Found: C, 76.13; H, 4.62; N, 7.11; S, 8.11 %.

5-(4-chlorophenyl)-4,7-diphenyl-1H-pyra[2,3-d]pyrimidine-2(5H)-thione (16b). Formed as pale yellow crystals from ethanol; yield (82%); m.p. 104—106 °C; \(^1\)H—NMR (DMSO—d\(_6\)) \(\delta\): 5.12—5.15 (d, 1H, CH—oliffin), 5.37—5.66 (d, 1H, 4H—pyrane), 7.03—9.90 (m, 14H, aromatic H), 10.00 (s, 1H, NH); IR (KBr) \(\nu\) cm\(^{-1}\): 3194 (NH), 3050 (CH—arom), 2950 (CH—aliph) cm\(^{-1}\); MS: \(m/z\) (%): 428 (M\(^+\)), Anal. calcd for C\(_{25}\)H\(_{17}\)ClN\(_2\)OS (428): C, 70.00; H, 3.99; N, 6.53; Cl, 8.27; S, 7.48; Found: C, 69.99; H, 3.97; N, 6.52; Cl, 8.26; S, 7.47 %.

5-(4-methoxyphenyl)-4,7-diphenyl-1H-pyra[2,3-d]pyrimidine-2(5H)-thione (16c).

Formed as pale yellow crystals from ethanol; yield (72%); m.p. 98—100 °C; \(^1\)H—NMR (DMSO—d\(_6\)) \(\delta\): 3.84 (s, 3H, OCH\(_3\)), 3.91—3.94 (d, 1H, CH—oliffin), 5.32—5.34 (d, 1H, 4H—pyrane), 6.97—8.10 (m, 14H, aromatic H), 9.65 (s, 1H, NH); IR (KBr) \(\nu\) cm\(^{-1}\): 3272 (NH), 3050 (CH—arom) cm\(^{-1}\); MS: \(m/z\) (%): 425 (M\(^+\)+1), Anal. calcd for C\(_{26}\)H\(_{20}\)N\(_2\)O\(_2\)S (424): C, 73.56; H, 4.75; N, 6.60; S, 7.55; Found: C, 73.57; H, 4.76; N, 6.61; S, 7.53 %.

procedure for the preparation of pyranopyrimidine derivatives (20).

A mixture of dihydropyrimidinone derivatives (4) (2.04 g; 0.01 mol) and formaldehyde/malononitrile (0.01 mol) in ethanol (50 mL) containing catalytic amount of piperidine was heated under reflux for 24 hrs, then left to cool and poured into crushed ice then acidified with HCl. The solid product was filtered off, washed with water and crystallized from the proper solvent to give (20).

7-Amino-4-phenyl-2-thioxo-2,5-dihydro-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile (20).

Formed as brown crystals from ethanol; yield (73%); m.p. 258—260 °C; \(^1\)H—NMR (DMSO—d\(_6\)) \(\delta\): 4.12 (s, 2H, CH\(_2\)), 6.72 (s, 2H, NH\(_2\)), 6.99—8.86 (m, 5H, aromatic H), 12.00 (hump, 1H, NH); IR (KBr) \(\nu\) cm\(^{-1}\): 3330, 3179 (NH\(_2\)), 2926
procedure for the preparation of pyranopyrimidine carbonitrile derivatives (24a,b).

A mixture of dihydropyrimidinone derivatives (4) (2.04 g; 0.01 mol) and 2-ethoxymethylene malononitrile (21a), ethyl-2-cyano-3-ethoxyacrylate (21b) (0.01 mol) in ethanol (50 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 excess of water and crystallized from the proper solvent to give the pyranopyrimidine carbonitrile derivative (24a,b).

7-Imino-4-phenyl-2-thioxo-2,7-1H-pyran-2,3-d|pyrimidine-6-carbonitrile (24a). Formed as brown crystals from ethanol; yield (78%); m.p.288—290 °C; $^1$H—NMR (DMSO—d$_6$) $\delta$ : 1.63 (s, H, NH); 1.90 (s, 1H, NH), 6.40—7.01 (m, 6H, aromatic H and CH—oliffinic); IR (KBr) $\nu$ cm$^{-1}$: 3420, 3339 (2NH), 2924 (CH—aliph), 2210 (CN) cm$^{-1}$; MS: $m/z$ (%) 280 (M$^+$), Anal.Calcd for C$_{14}$H$_8$N$_4$OS (280): C, 59.99; H, 2.88; N, 19.99; S, 11.44; Found: C, 60.00; H, 2.89; N, 20.01; S, 11.42 %.

7-Oxo-4-phenyl-2-thioxo-2,7-1H-pyran-2,3-d|pyrimidine-6-carbonitrile (24b). Formed as yellow crystals from ethanol; yield (83%); m.p.108—110 °C; $^1$H—NMR (DMSO—d$_6$) $\delta$ : 1.56 (s, 1H, NH), 5.09 (s, 1H, CH—oliffin), 7.01—7.77 (m, 5H, aromatic H); IR (KBr) $\nu$ cm$^{-1}$: 3382 (NH), 2955 (CH—aliph), 2201 (CN), 1616 (C=O) cm$^{-1}$; MS: $m/z$ (%) 281 (M$^+$), Anal.

Calcld for C$_{14}$H$_7$N$_2$OS (281): C, 59.78; H, 2.51; N, 14.94; S, 11.40; Found: C, 59.79; H, 2.53; N, 14.95; S, 11.39 %.

procedure for the preparation of chromenopyrimidinethione derivatives (29a-d).

A mixture of dihydropyrimidinone derivatives (4) (2.04 g; 0.01 mol) and benzylidenecyclohexanone derivatives (25a-d) (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 (29a-d).

4,5-diphenyl-6,7,8,9-tetrahydro-1H-chromeno[2,3-d]pyrimidine-2(5H)-thione (29a).

Formed as pale yellow crystals from ethanol; yield (84%); m.p.105—107 °C; $^1$H—NMR (CDCl$_3$) $\delta$: 1.22—1.40 (m, 4H, 2CH$_2$), 1.43—3.33 (m, 4H, 2CH$_2$), 3.71 (s, 1H, 4H—pyrane), 6.95—7.56 (m, 10H, aromatic H), 7.81 (s, 1H, NH); IR (KBr) $\nu$ cm$^{-1}$: 3420 (NH), 3056 (CH—arom), 2932 (CH—aliph) cm$^{-1}$; MS: $m/z$ (%) 372 (M$^+$), Anal. Calcd for C$_{23}$H$_{20}$N$_2$S (372): C, 74.16; H, 5.41; N, 7.52; S, 8.61; Found: C, 74.17; H, 5.42; N, 7.50; S, 8.60 %.

5-(4-chlorophenyl)-4-phenyl-6,7,8,9-tetrahydro-1H-chromeno[2,3-d]pyrimidine-2(5H)-thione (29b).

Formed as pale yellow crystals from ethanol; yield (86%); m.p.111—113 °C; $^1$H—NMR (CDCl$_3$) $\delta$: 0.75—1.97 (m, 4H, 2CH$_2$), 2.09—3.93 (m, 4H, 2CH$_2$), 4.37 (s, 1H, 4H—pyrane), 6.67—8.01 (m, 9H, aromatic H); 9.35 (s, 1H, NH); IR (KBr) $\nu$ cm$^{-1}$: 3418 (NH), 3058 (CH—arom), 2932 (CH—aliph) cm$^{-1}$; MS: $m/z$ (%) 407 (M$^+$+1), Anal. Calcd for C$_{23}$H$_{19}$ClN$_2$OS (406): C, 67.89; H, 4.71;
N, 6.88; Cl, 8.71; S, 7.88; Found: C, 67.90; H, 4.72; N, 6.90; Cl, 8.70; S, 7.87%.

5-(4-methoxyphenyl)-4-phenyl-6,7,8,9-tetrahydro-1H-chromeno[2,3-d]pyrimidine-2(5H)-thione (29c).

Formed as yellow crystals from ethanol; yield (81%); m.p.140–142 °C; ¹H—NMR (CDCl₃) δ: 1.79–2.18 (m, 4H, 2CH₂), 2.90–2.94 (m, 4H, 2CH₂), 3.85 (s, 3H, OCH₃), 3.89 (s, 1H, 4H—pyrane), 6.92–7.78 (m, 10H, aromatic H and NH); IR (KBr) ν cm⁻¹: 3381 (NH), 2938 (CH—aliph) cm⁻¹; MS: m/z (%) 402 (M⁺), Anal. calcd for C₂₄H₂₂N₂O₂S (402): C, 71.62; H, 5.51; N, 6.96; S, 7.97%.

5O(4Ohydroxyphenyl)O4OphenylO6,7,8,9OtetrahydroO1H—NMR (CDCl₃) δ: 1.79–2.18 (m, 4H, 2CH₂), 2.90–2.94 (m, 4H, 2CH₂), 3.85 (s, 3H, OCH₃), 3.89 (s, 1H, 4H—pyrane), 6.92–7.78 (m, 10H, aromatic H and NH); IR (KBr) ν cm⁻¹: 3381 (NH), 2938 (CH—aliph) cm⁻¹; MS: m/z (%) 402 (M⁺), Anal. calcd for C₂₄H₂₂N₂O₂S (402): C, 71.62; H, 5.51; N, 6.96; S, 7.97%.

procedure for the preparation of compound (31).

A mixture of (11b) (3.92 g; 0.01 mol) and 2-chloroacetyl chloride (30) (0.01 mol) in dioxane (50 mL) was heated under reflux for 4 hrs. The reaction mixture was allowed to cool. The separated solid was filtered, washed with ethanol and crystallized from the proper solvent to give (32).

Method (B):

A mixture of (31) (4.29 g; 0.01 mol) and ammonium acetate was fused for 6 hrs. The reaction mixture was allowed to cool, then triturated with ethanol.

The separated solid was filtered off, washed with water and crystallized from the proper solvent to give (32).

8-(chloromethyl)-5(4-chlorophenyl)-4-phenyl-2-thioxo-5,7-dihydro-1H-pyrano[2,3-d:6,5-d']dipyrimidin6(2H)-one (32).

Formed as pale yellow crystals from ethanol; yield (71%); m.p.320–322 °C; ¹H—NMR (CDCl₃) δ: 1.59 (s, 1H, NH), 2.18 (s, 1H, NH), 3.50 (s, 2H, CH₂), 3.77 (s, 1H, 4H—pyrane), 7.17–7.61 (m, 9H, aromatic H); MS: IR (KBr) ν cm⁻¹: 3143 (NH), 3045 (CH—arom), 2807 (CH—aliph), 1758 (CO) cm⁻¹; MS: m/z (%) 469 (M⁺), Anal. calcd for C₂₂H₁₄Cl₂N₄O₂S
Elian, et al. (469): C, 56.30; H, 3.01; N, 11.94; Cl, 15.11; S, 6.83; Found: C, 56.29; H, 3.00; N, 11.92; Cl, 15.10; S, 6.82 %.

**procedure for the preparation of compound (33).**

A mixture of (11b) (3.92 g; 0.01 mol) and 2-benzylidenemalononitrile (6a) (0.01 mol) in ethanol (50 mL) containing catalytic amount of pipridine was heated under reflux for 8 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 (33).

6-amino-5-(4-chlorophenyl)-4,8-diphenyl-2-thioxo-2,5-dihydro-1H-pyrido[3',2':5,6]pyrano[2,3-d]pyrimidine-7-carbonitrile (33).

Formed as pale yellow crystals from ethanol; yield (77%); m.p.110—112 °C; \(^1\)H—NMR (CDCl\(_3\)) \(\delta\): 4.60 (s, 1H, 4H—pyrane), 6.19 (s, 2H, NH\(_2\)), 7.31—7.96 (m, 14H, aromatic H), 9.31 (s, 1H, NH); IR (KBr) \(\nu\) cm\(^{-1}\): 3331, 3203 (NH\(_2\)), 3087 (CH—arom), 2933 (CH—aliph), 2190 (CN) cm\(^{-1}\); MS: \(m/z\) (%), Anal. calcd for C\(_{29}\)H\(_{18}\)ClN\(_5\)OS (520): C, 66.98; H, 3.49; N, 13.47; Cl, 6.82; S, 6.17; Found: C, 66.97; H, 3.47; N, 13.46; Cl, 7.90; S, 7.14 %.

**procedure for the preparation of compound (34).**

A mixture of (11b) (3.92 g; 0.01 mol) and DMF—DMA (0.01 mol) in xylene (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 the proper solvent to give (34).

N’-(5-(4-chlorophenyl)-6-cyano-4-phenyl-2-thioxo-2,5-dihydro-1H-pyranoyl)[2,3-d]pyrimidin-7-yl)-N,N-dimethylformimide (34).

Formed as pale yellow crystals from ethanol; yield (81%); m.p.210—212 °C; \(^1\)H—NMR (DMSO—d\(_6\)) \(\delta\): 3.28 (s, 3H, CH\(_3\)), 3.43 (s, 3H, CH\(_3\)), 4.27 (s, 1H, 4H—pyrane), 7.36—7.61 (m, 11H, aromatic H, N=CH and NH); IR (KBr) \(\nu\) cm\(^{-1}\): 3340 (NH), 2926 (CH—aliph), 2210 (CN) cm\(^{-1}\); MS: \(m/z\) (%) 447 (M\(^+\)), Anal. calcd for C\(_{23}\)H\(_{18}\)ClN\(_2\)OS (447): C, 61.67; H, 4.05; N, 15.63; Cl, 7.91; S, 7.16; Found: C, 61.68; H, 4.06; N, 15.64; Cl, 7.90; S, 7.14 %.

**procedure for the preparation of compound (35).**

**Method (A):**

A mixture of (11b) (3.92 g; 0.01 mol) and formamide (0.01 mol) in xylene (30 ml) 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 (35).

6-Amino-5-(4-chlorophenyl)-4-phenyl-1,5-dihydro-2H-pyrimido[5',4':5,6]-pyrano[2,3-d]pyrimidine-2-thione (35).

Formed as brown crystals from ethanol; yield (79%); m.p.150—152 °C; \(^1\)H—NMR (DMSO—d\(_6\)) \(\delta\): 4.40 (s, 1H, 4H—pyrane), 7.36 (s, 1H, pyrimidine—H), 8.16—9.70 (m, 9H, aromatic H), 10.63 (s, 1H, NH\(_2\)); IR (KBr) \(\nu\) cm\(^{-1}\): 3460, 3440 (NH\(_2\)), 3202 (NH), 2902 (CH—aliph) cm\(^{-1}\); MS: \(m/z\) (%) 421 (M\(^+\)+1), Anal. calcd for C\(_{21}\)H\(_{14}\)ClN\(_3\)OS (420): C, 60.07; H, 3.36; N, 16.68; Cl, 8.44; S, 7.64; Found: C,
60.08; H, 3.37; N, 16.70; Cl, 8.43; S, 7.63 %.

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البيريميدين ثيون كأساس في التحضيرات غير المتنازلة الحلقية: تحضير بيرانو(3,4,5)-بيريميدين، كرومينو (2,3-دي) بيريميدين، بيريدو (3,4,5)-بيرانوبريميدين وبريميدو (4,5)-بيرانو(3,4-دي) بيريميدين

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مجموعة جديدة من مشتقات الثيوكوبيريميدين، بيران، بيرانوبريميدين وبرانوبريميدين ذات نشاط بيولوجي متوقع. تم تحضيرها من خلال تفاعل فينيل-2-ثيوكوبيرامينو(3,4-دي)-بيريميدين من مجموعات ثيوكوبيرامينو(3,4-دي)-بيريميدين وبريميدو (4-كرومينو (2,3-دي)-بيريدين، بيريدين (2,3-دي)-بيريدين، بيريدين (2,3-دي)-بيريدين (2,3-دي)-بيريدين. تمت أتميم ترتيبها من خلال تحايل تحت الحمراء والزئين التوحيدي المغناطيسي. الأدبيات. الكتلة.

الكلمات الإسترشادية: ثيوكوبيريميدين، بيران، بيرانوبريميدين وبرانوبريميدين.

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