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PYRIMIDINETHIONES AS BUILDING BLOCKS IN HETEROCYCLIC SYNTHESIS: SYNTHESIS OF PYRANO[2,3-D]PYRIMIDINE, CHROMENO[2,3-D]PYRIMIDINE, PYRIDO[3',2':5,6]PYRANO[2,3-B]PYRIDINE AND PYRIMIDO[5',4':5,6]PYRANO[2,3-D]PYRIMIDINE

Mohamed A. Elian, Ibrahim S. A. Hafiz, Mohamed A. M. Abdel Reheim

Dept. of Chemistry, Faculty of Education, Suez Canal University, El-Arish, Egypt.

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-pyrano[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-pyrans, 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-pyrans and their derivatives are of considerable interest due to their pharmacological activities **(Green *et al*, 1995),** such as spasmolytic, diuretic, anticoagulant, anticancer, and antianaphylactic activity **(abdelrazek *et al,* 2007; Bonsignore *et al,* 1993; Witte *et al,* 1986).** In addition, 4H-pyrans are useful intermediates for synthesis of various compounds, such as pyranopyridine derivatives **(Lei and Hu, 2011)** and pyranopyrimidines **(Quintela *et al,* 1995).**

Also, various pyranopyrimidines exhibit antimicrobial **(Eid *et al,* 2004),** antibacterial **(Abd El-Wahab, 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 antiphologisti 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 (5*H*)-one as starting materials aiming to develop a new synthetic route for synthesing new heterocyclic derivatives.

RESULTS AND DISCUSSIONS

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

established via nspection of its IR, ^{1}H-NMR and mass spectra [Mahmoud et al, 2012]. The isomeric structure **5** can be isolated in lower yield (5%) (Scheme 1).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.

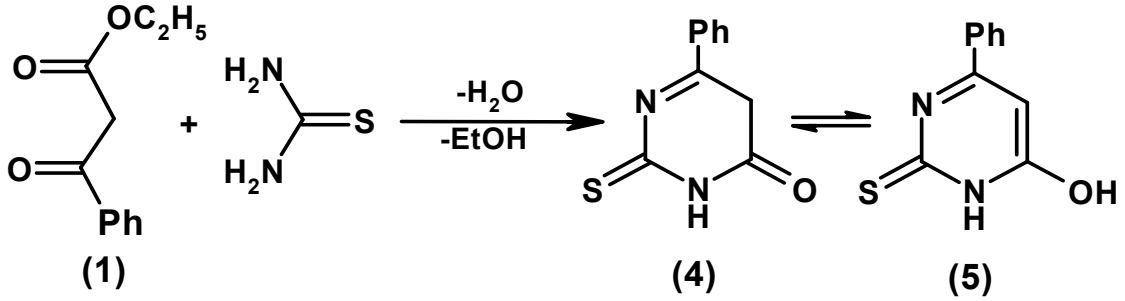
Thus, Compounds **11a-e** were synthesized in quantitative yield, when **4** is allowed to react with arylidenemalononitrile derivatives **6a-e**under reflux in ethanol and in the presence of catalytic amounts of pipridine.

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-c** in the presence of piperidine led to the formation of pyranopyrimidinethione derivatives **16a-c [El-saied *et al,* 2004**] (Scheme 2).A mixture of formaldehyde and malononitrile was reacted with compound **4** in refluxing ethanol/pipridine 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 ethoxymethylenemalononitrile, 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-4-phenyl-2-thioxo-2,5-dihydro-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile 11b for the synthesis of some novel heterocycles in corporating pyrimidinethione moiety. So, when compound 11b allowed to react with chloroacetylchloride 30 in refluxing dioxane it afforded the novel 2-chloroacetimidate derivatives 31 in acceptable yield (80%).



Scheme 1

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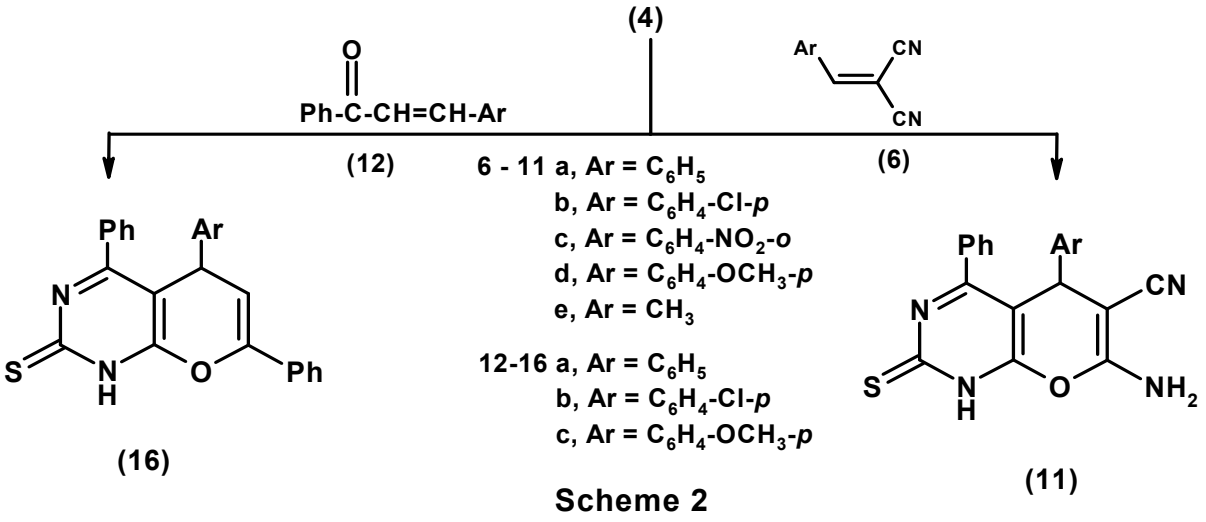


Scheme 2

The structure of compound 31 was established on the basis of analytical and spectral data. Furthermore the reaction of 11b with chloroacetylchloride 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 dimethylformamidedimethylacetal (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).

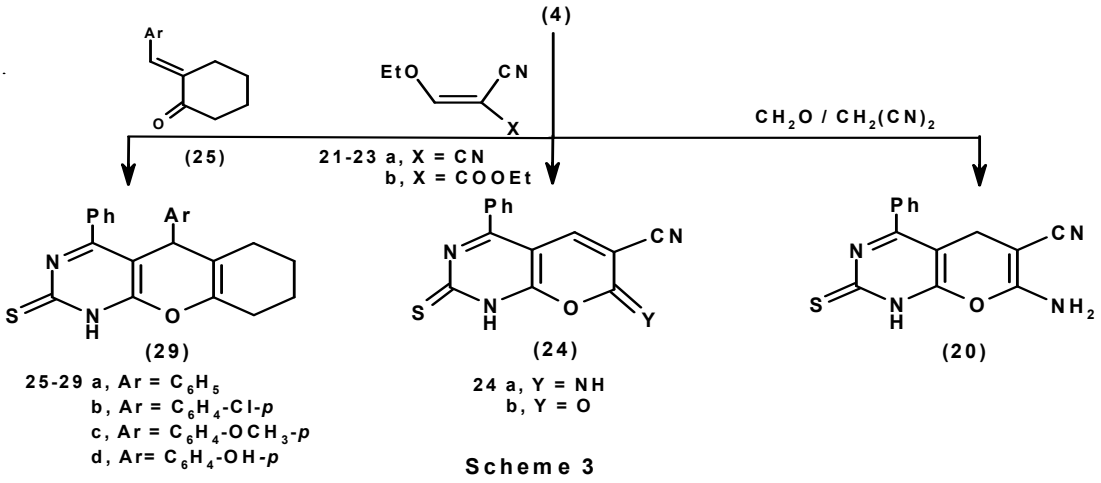
EXPERIMENTS

Melting points were determined using a Büchi apparatus and are uncorrected. The purity of compound was confirmed by TLC using Merck silica gel $60F_{254}$ 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}. ^1H 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 (δ) relative to TMS as a standard.

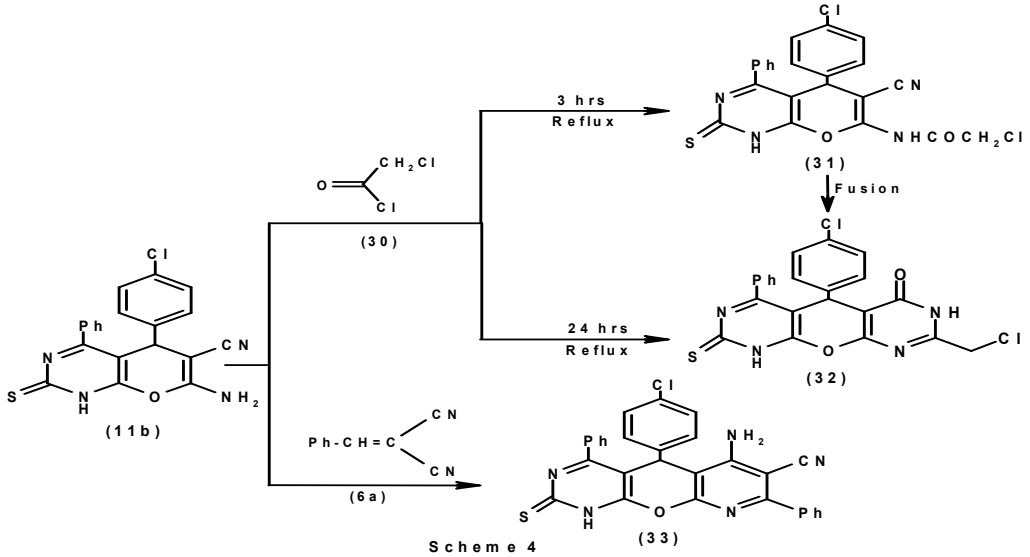
The mass spectra were recorded with a HP D5988 A 1000 MHz instrument (Hewlett-Packard). Elemental analyses were performed at the Microanalytical Centre at the Faculty of Science, Cairo University, Egypt.

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

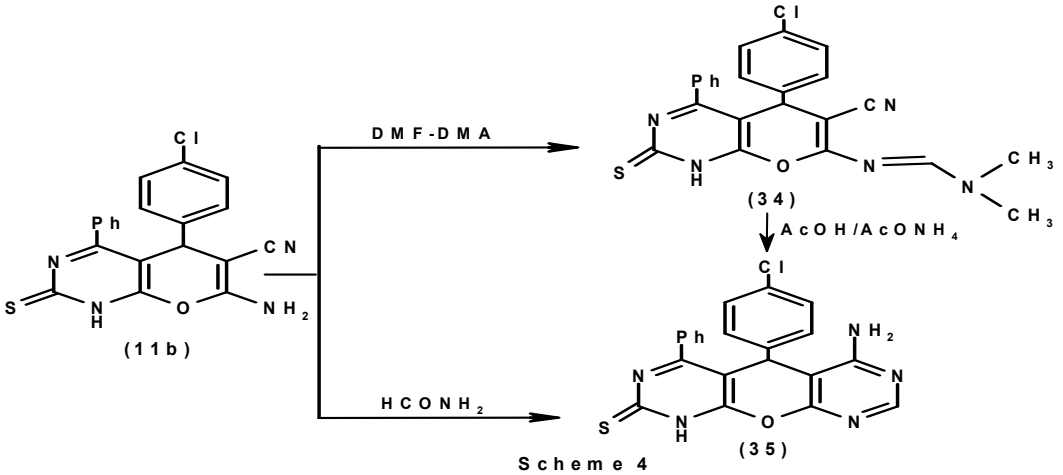
A mixture of thiourea (0.76 g, 0.01 mol) and ethyl benzoylacetate (1.92 g, 0.01 mol) was stirred overnight without solvent for 24 hrs at room temperature. The solid product formed was filtered off, washed with diethyl ether and crystallized from ethanol to give **(4, 5).**



Scheme 3



Scheme 4



Scheme 4

6-phenyl-2-thioxo-2,3-dihydropyrimidin-4(5*H*)-one (4). It was obtained as white crystals yield (83%); m.p.145—147°C; ^{1}H—NMR (DMSO—d_6) δ: 4.17 (s, 2H, CH_2), 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 $C_{10}H_8N_2OS$ (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 %.

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

It was obtained as yellow crystals yield (5%); m.p.240—242 °C; ^{1}H—NMR (DMSO—d_6) 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 $C_{10}H_8N_2OS$ (204): C, 58.80; H, 3.95; N, 13.72; S, 15.70; Found: C, 58.81; H, 3.96; N, 13.74; 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-dihydro-1*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile (11a).

Formed as white crystals from ethanol; yield (82%); m.p.108—110 °C; ^{1}H—NMR (DMSO—d_6) δ: 4.97 (s, 1H, 4H—pyrane), 6.13 (s, 2H, NH_2); 9.73 (s, 1H, NH), 7.05—7.79 (m, 10H, aromatic H); IR (KBr) ν cm^{-1}: 3329, 3203 (NH_2), 3050 (CH—arom), 2934 (CH—aliph), 2185 (CN) cm^{-1}; MS: *m/z (%)* 359 (M^++1), Anal. calcd for $C_{20}H_{14}N_4OS$ (358): 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-1*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile (11b). Formed as yellow crystals from ethanol; yield (84%); m.p.186—188 °C; ^{1}H—NMR (DMSO—d_6) δ: 5.02 (s, 1H, 4H—pyrane), 6.15 (s, 2H, NH_2), 7.00—7.84 (m, 10H, aromatic H and NH); IR (KBr) ν cm^{-1}: 3471, 3332 (NH_2), 3226 (NH), 2924 (CH—aliph), 2218 (CN) cm^{-1}; MS: *m/z (%)* 392 (M^+), Anal. calcd for $C_{20}H_{13}ClN_4OS$ (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-1*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile (11c). Formed as pale yellow crystals from ethanol; yield (78%); m.p.150-152 °C; ^{1}H—NMR ($CDCl_3$) δ: 4.38 (s, 1H, 4H—pyrane), 6.62 (s, 2H, NH_2), 6.95—8.54 (m, 9H, aromatic H), 9.28 (s, 1H, NH); IR (KBr) ν cm^{-1}: 3336, 3200 (NH_2), 2936 (CH—aliph), 2191 (CN) cm^{-1}; MS: *m/z (%)* 403 (M^+), Anal. calcd for $C_{20}H_{13}N_5O_3S$ (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-1*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile (11d).

Formed as green crystals from ethanol; yield (70%); m.p.180-182 °C; ^{1}H—NMR (DMSO—d_6) δ: 3.71 (s, 3H, OCH_3), 3.84 (s, 1H, 4H—pyrane), 7.02—7.85 (m, 12H, aromatic H+NH_2); IR (KBr) ν cm^{-1}: 3401, 3214 (NH_2), 2933 (CH—aliph), 2197 (CN) cm^{-1}; MS: *m/z (%)* 388 (M^+), Anal. calcd for $C_{21}H_{16}N_4O_2S$ (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-1*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile (11e).

Formed as pale green crystals from ethanol; yield (78%);m.p.170—172 ^{o}C; ^{1}H—NMR (DMSO—d_6) δ: 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) ν cm^{-1}: 3349, 3228 (NH_2), 2932 (CH—aliph), 2193 (CN) cm^{-1}; MS: *m/z (%)* 296 (M^+), Anal. calcd for $C_{15}H_{12}N_4OS$ (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 pipridine 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-pyrano[2,3-d]pyrimidine-2(5*H*)-thione (16a).

Formed as pale yellow crystals from ethanol; yield (88%); m.p.100—102 ^{o}C; ^{1}H—NMR (DMSO—d_6) δ: 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) ν cm^{-1}: 3181 (NH), 3083 (CH—arom), 2962 (CH—aliph) cm^{-1}; MS: *m/z (%)* 394 (M^+), Anal. calcd for $C_{25}H_{18}N_2OS$ (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-1*H*-pyrano[2,3-*d*]pyrimidine-2(5*H*)-thione (16b). Formed as pale yellow crystals from ethanol; yield (82%); m.p.104—106 ^{o}C; ^{1}H—NMR (DMSO—d_6) δ: 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) ν cm^{-1}: 3194 (NH), 3050 (CH—arom), 2950 (CH—aliph) cm^{-1}; MS: *m/z (%)* 428 (M^+), Anal. calcd for $C_{25}H_{17}ClN_2OS$ (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-1*H*-pyrano[2,3-*d*]pyrimidine-2(5*H*)-thione (16c).

Formed as pale yellow crystals from ethanol; yield (72%); m.p.98—100 ^{o}C; ^{1}H—NMR (DMSO—d_6) δ: 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) ν cm^{-1}: 3272 (NH), 3050 (CH—arom) cm^{-1}; MS: *m/z (%)* 425 (M^++1), Anal. calcd for $C_{26}H_{20}N_2O_2S$ (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-1*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile(20).

Formed as brown crystals from ethanol; yield (73%); m.p.258—260 ^{o}C; ^{1}H—NMR (DMSO—d_6) δ : 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) ν cm^{-1}: 3330, 3179 (NH_2), 2926

(CH—aliph), 2203 (CN) cm^{-1}; MS: *m/z (%)* 283 (M^++1), Anal. calcd for $C_{14}H_{10}N_4OS$ (282): C, 59.56; H, 3.57; N, 19.85; S, 11.36; Found: C, 59.55; H, 3.55; N, 19.84; S, 11.34 %.

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-2,7-1*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile (24a). Formed as brown crystals from ethanol; yield (78%); m.p.288—290 ^oC; ^1H—NMR (DMSO—d_6) δ : 1.63 (s, H, NH); 1.90 (s, 1H, NH), 6.40—7.01 (m, 6H, aromatic H and CH—oliffinic); IR (KBr) ν cm^{-1}: 3420, 3339 (2NH), 2924 (CH—aliph), 2210 (CN) cm^{-1}; MS: *m/z (%)* 280 (M^+), Anal.Calcd for $C_{14}H_8N_4OS$ (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-2,7-1*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile (24b). Formed as yellow crystals from ethanol; yield (83%); m.p.108—110 ^oC; ^1H—NMR (DMSO—d_6) δ : 1.56 (s, 1H, NH), 5.09 (s, 1H, CH—oliffin), 7.01—7.77 (m, 5H, aromatic H); IR (KBr) ν cm^{-1}: 3382 (NH), 2955 (CH—aliph), 2201 (CN), 1616 (C=O) cm^{-1}; MS: *m/z (%)* 281 (M^+), Anal. Calcd for $C_{14}H_7N_3O_2S$ (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-1*H*-chromeno[2,3-*d*]pyrimidine-2(5*H*)-thione (29a).

Formed as pale yellow crystals from ethanol; yield (84%); m.p.105—107 ^oC; ^1H—NMR ($CDCl_3$) δ: 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) ν cm^{-1}: 3420 (NH), 3056 (CH—arom), 2932 (CH—aliph) cm^{-1}; MS: *m/z (%)* 372 (M^+), Anal. Calcd for $C_{23}H_{20}N_2OS$ (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-1*H*-chromeno[2,3-*d*]pyrimidine-2(5*H*)-thione (29b).

Formed as pale yellow crystals from ethanol; yield (86%); m.p.111—113 ^oC; ^1H—NMR ($CDCl_3$) δ: 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) ν cm^{-1}: 3418 (NH), 3058 (CH—arom), 2932 (CH—aliph) cm^{-1}; MS: *m/z (%)* 407 (M^++1), Anal. calcd for $C_{23}H_{19}ClN_2OS$ (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-1*H*-chromeno[2,3-*d*]pyrimidine-2(5*H*)-thione (29c).

Formed as yellow crystals from ethanol; yield (81%); m.p.140—142 ^{o}C; ^{1}H—NMR ($CDCl_3$) δ: 1.79—2.18 (m, 4H, $2CH_2$), 2.90—2.94 (m, 4H, $2CH_2$), 3.85 (s, 3H, OCH_3), 3.89 (s, 1H, 4H—pyrane), 6.92—7.78 (m, 10H, aromatic H and NH); IR (KBr) cm^{-1}: 3381 (NH), 2938 (CH—aliph) cm^{-1}; MS: *m/z (%)* 402 (M^+), Anal. Calcd for $C_{24}H_{22}N_2O_2S$ (402): C, 71.62; H, 5.51; N, 6.96; S, 7.97; Found: C, 71.61; H, 5.50; N, 6.94; S, 7.95 %.

5-(4-hydroxyphenyl)-4-phenyl-6,7,8,9-tetrahydro-1*H*-chromeno[2,3-*d*]pyrimidine2(5*H*)thione (29d).

Formed as pale yellow crystals from ethanol; yield (80%); m.p.102—104 ^{o}C; ^{1}H—NMR (DMSO— d_6) δ: 0.88—1.56 (m, 4H, $2CH_2$), 1.90—2.40 (m, 4H, $2CH_2$), 3.73 (s, 1H, 4H—pyrane), 6.65—7.42 (m, 9H, aromatic H), 8.25 (s, 1H, NH), 9.12 (s, 1H, OH); IR (KBr) ν cm^{-1}: 3339 (NH), 3060 (CH—arom), 2932 (CH—aliph) cm^{-1}; MS: *m/z (%)* 388 (M^+), Anal. calcd for $C_{23}H_{20}N_2O_2S$ (388): C, 71.11; H, 5.19; N, 7.21; S, 8.25; Found: C, 71.10; H, 5.18; N, 7.20; S, 8.24 %.

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 (30 mL) was heated under reflux for 3 hrs.

The reaction mixture was allowed to cool. The separated solid was filtered, washed with ethanol and crystallized from the proper solvent to give **(31)**.

2-chloro-N-(5-(4-chlorophenyl)-6-cyano-4-phenyl-2-thioxo-2,5-dihydro-1*H*-pyrano[2,3-*d*]pyrimidin-7-yl)acetamide (31).

Formed as pale yellow crystals from ethanol; yield (80%); m.p.100—102 ^{o}C; ^{1}H—NMR (DMSO—d_6) δ: 4.31 (s, 2H, CH_2), 5.23 (s, 1H, 4H—pyrane), 6.94—8.29 (m, 9H, aromatic H); 10.17 (s, 1H, NH); 11.76 (s, 1H, NH); IR (KBr) ν cm^{-1}: 3330, 3212 (2NH), 3065 (CH—arom), 2956 (CH—aliph), 2214 (CN), 1731 (CO) cm^{-1}; MS: *m/z (%)* 469 (M^+), Anal. calcd for $C_{22}H_{14}Cl_2N_4O_2S$ (469): C, 56.30; H, 3.01; N, 11.94; Cl, 15.11; S, 6.83; Found: C, 56.29; H, 3.00; N, 11.93; Cl, 15.10; S, 6.82 %.

procedure for the preparation of compound (32). Method (A):

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 24 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-1*H*-pyrano[2,3-d:6,5-*d′*]dipyrimidin6(2*H*)-one (32).

Formed as pale yellow crystals from ethanol; yield (71%); m.p.320—322^{o}C; ^{1}H—NMR ($CDCl_3$) δ: 1.59 (s, 1H, NH), 2.18 (s, 1H, NH), 3.50 (s, 2H, CH_2), 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 $C_{22}H_{14}Cl_2N_4O_2S$

(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-1*H*-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 ^{o}C; ^{1}H—NMR ($CDCl_3$) δ: 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) ν cm^{-1}: 3331, 3203 (NH_2), 3087 (CH—arom), 2933 (CH—aliph), 2190 (CN) cm^{-1}; MS: *m/z (%)* 520 (M^+), Anal. calcd for $C_{29}H_{18}ClN_5OS$ (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, 6.82; S, 6.17 %.

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. The separated solid was filtered, washed with ethanol and crystallized from the proper solvent to give **(34)**.

N'-(5-(4-chlorophenyl)-6-cyano-4-phenyl-2-thioxo-2,5-dihydro-1*H*-pyrano[2,3-*d*]pyrimidin-7-yl)-*N*,*N*-dimethylformimidamide (34).

Formed as brown crystals from ethanol; yield (81%); m.p.210—212 ^{o}C; ^{1}H—NMR (DMSO—d_6) δ: 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) ν cm^{-1}: 3340 (NH), 2926 (CH—aliph), 2210 (CN) cm^{-1}; MS: *m/z (%)* 447 (M^+), Anal. calcd for $C_{23}H_{18}ClN_5OS$ (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)**.

Method (B):

A mixture of **(34)** (4.47 g; 0.01 mol) and AcOH/$AcONH_4$ 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 **(35)**.

6-Amino-5-(4-chlorophenyl)-4-phenyl-1,5-dihydro-2*H*-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 ^{o}C; ^{1}H—NMR (DMSO— d_6) δ: 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), 12.10 (s, 2H, NH_2); IR (KBr) ν cm^{-1}: 3460, 3440 (NH_2), 3202 (NH), 2902 (CH—aliph) cm^{-1}; MS: *m/z (%)* 421 (M^++1), Anal. calcd for $C_{21}H_{14}ClN_5OS$ (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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الملخص العربي

البيريميدين ثيون كأساس في التحضيرات غير المتجانسة الحلقة: تحضير بيرانو(٣،٢-د) بيريميدين، كرومينو (٣،٢-د) بيريميدين، بيريدو(٣،٢،٥:٦) بيرانوبيريدين وبيريميدو(٥،٤،٦:٥) بيرانو(٣،٢-د) بيريميدين

محمد أحمد عليان، إبراهيم سعد عبد الحافظ، محمد أحمد محمود عبد الرحيم

قسم الكيمياء، كلية التربية، جامعة قناة السويس، العريش، مصر

مجموعة جديدة من مشتقات الثيوكسوبيريميدين، بيران، بيرانوبيريدين وبيرانوبيريميدين ذات نشاط بيولوجى متوقع تم تحضيرها من خلال تفاعل ٦-فينيل-٢-ثيوكسو-٣،٢-ثنائى هيدروبيريميدين-٤ (٥-هيدرو)-٦-كربونيتريل ٤ و٧امينو-٥-(٤-كلوروفينيل)-٤-فينيل-٢-ثيوكسو-٥،٢-ثنائى هيدرو-١-هيدرو-بيرانو(٣،٢-د)بيريميدين-٦-كربونيتريل ١١ب مع بعض الكواشف الالكتروفيلية والنيوكليوفيلية. المركبات الجديدة التى تم تحضيرها تم اثبات تركيبها من خلال تحاليل تحت الحمراء، الرنين النووى المغناطيسى ومطياف الكتلة.

الكلمات الإسترشادية: ثيوكسوبيريميدين، بيران، بيرانوبيريدين وبيرانوبيريميدين.
