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Pyrimidinethione as a building block 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 derivatives

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Abstract: New heterocyclic compounds with expected biological activity have been prepared by reactions of 6-phenyl-2-thioxo-2,3-dihydropyrimidine-4(5*H*)-one (**4**) and 7-amino-5-(4-chlorophenyl)-4-phenyl-2-thioxo-2,5-dihydro-1*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile (**8b**) in the presence of an electrophilic or a nucleophilic reagent.

Keywords: pyranopyridine; pyranopyrimidine; 4*H*-pyrans; thioxopyrimidine.

Introduction

Pyrimidinethiones have been found to possess antimicrobial [1, 2], antitubercular [3], antitumor [4], and hypoglycemic activity [5]. However, 4*H*-pyrans are spasmolytic, diuretic, anticoagulant, anticancer, and antianaphylactic agents [6–9]. In addition, 4*H*-pyrans are useful intermediates for synthesis of fused pyranopyridines [10] and pyranopyrimidines [11]. Also, various pyranopyrimidines exhibit antimicrobial [12], antibacterial [13], antigenotoxic [14], antifungal [15–17], antithrombotic [18], analgesic, anti-inflammatory, and antiphologistic activity [19, 20]. In this paper we report the synthesis of new pyranopyrimidinethiones and chromenopyrimidinethiones.

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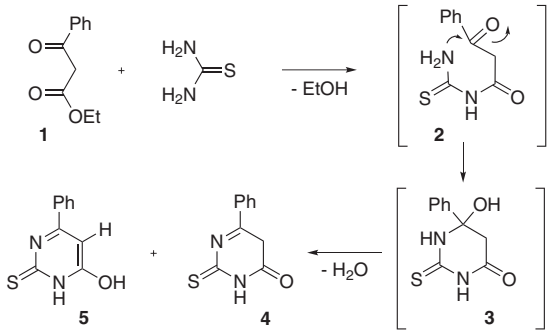
Results and discussion

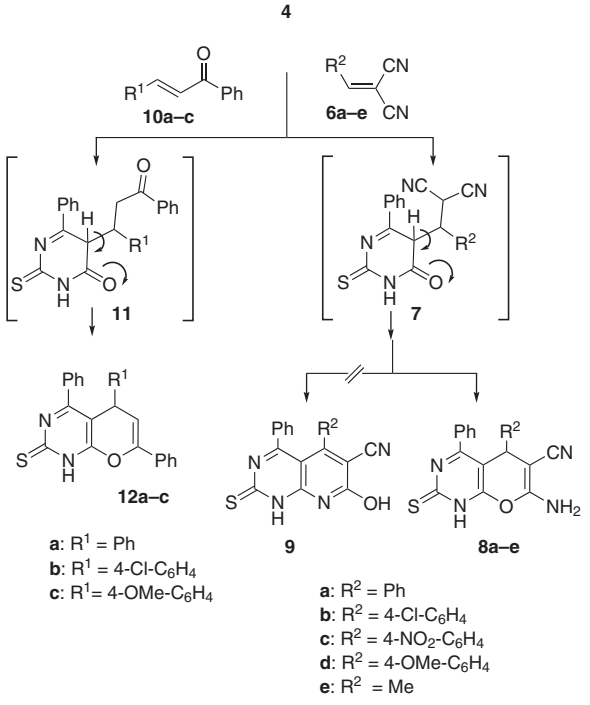
The reaction of ethyl benzoylacetate (**1**) with thiourea yielded a mixture of pyrimidinethione **4** as a major product and its tautomer **5** as a minor product [21], apparently through intermediates **2** and **3** (Scheme 1). Products **4** and **5** were isolated by silica gel chromatography but the mixture was used for the transformations described below. The mixture is referred to as compound **4**.

The active methylene group in compound **4** was exploited to synthesize novel heterocyclic compounds by reactions with electrophilic reagents. Thus, the pyrano[2,3-*d*]pyrimidine-6-carbonitriles **8a–e** were synthesized in an excellent yield upon treatment of **4** with arylidenemalononitriles **6a–e** in the presence of a catalytic amount of piperidine. The structures of compounds **8a–e** were established based on analytical and spectral data. Products **8a–e** are apparently formed via a Michael type addition of the active methylene group in pyrimidinethione **4** to the activated double bond in arylidenemalononitriles **6a–e** followed by intramolecular cyclization of the intermediate adducts **7** [21–23] (Scheme 2). The alternative products **9** were not found. In a similar manner, the reaction of **4** with α, β-unsaturated ketones **10a–c** in the presence of a catalytic amount of piperidine may result in the formation of the intermediate adducts **11**, which are precursors to the final pyranopyrimidinethiones **12a–c** [24].

A mixture of formaldehyde and malononitrile was allowed to react with compound **4** in refluxing ethanol in the presence of a catalytic amount of piperidine to give **14** [25, 26]. It can be suggested that compound **14** is formed by the addition of the active methylene group in **4** to the π-deficient center in an intermediate alkylidenenitrile followed by cyclization of the resultant

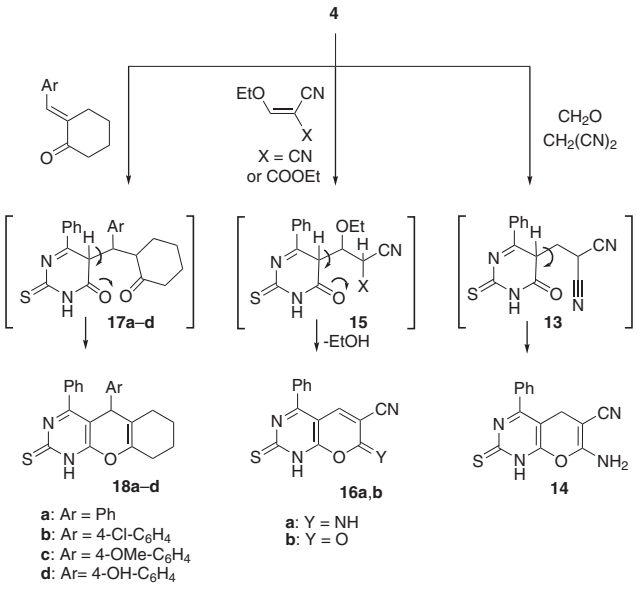


Scheme 1



Scheme 2

intermediate adducts **13** (Scheme 3). Pyranopyrimidines **16a,b** were synthesized by cyclocondensation of compound **4** with ethoxymethylenemalononitrile and ethyl 2-cyano-3-ethoxyacrylate, respectively, in refluxing ethanol in the presence of a catalytic amount of piperidine. Adducts **15** are the suggested intermediate products (Scheme 3). The given structures of **16a,b** are fully consistent with elemental analysis and spectral data. In a similar manner, cyclization of 2-(benzylidene) cyclohexanones with substrate **4** in ethanol at reflux in the presence of piperidine produced the corresponding chromenopyrimidinethiones **18a–d** [27]. Again, the formation of **18a–d** can be understood in terms of the Michael type addition of the active methylene group

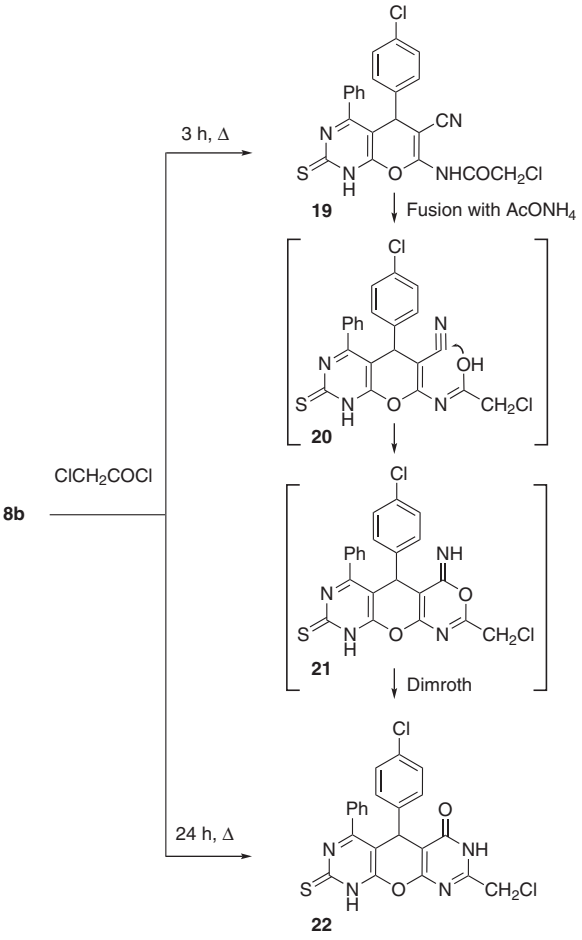


Scheme 3

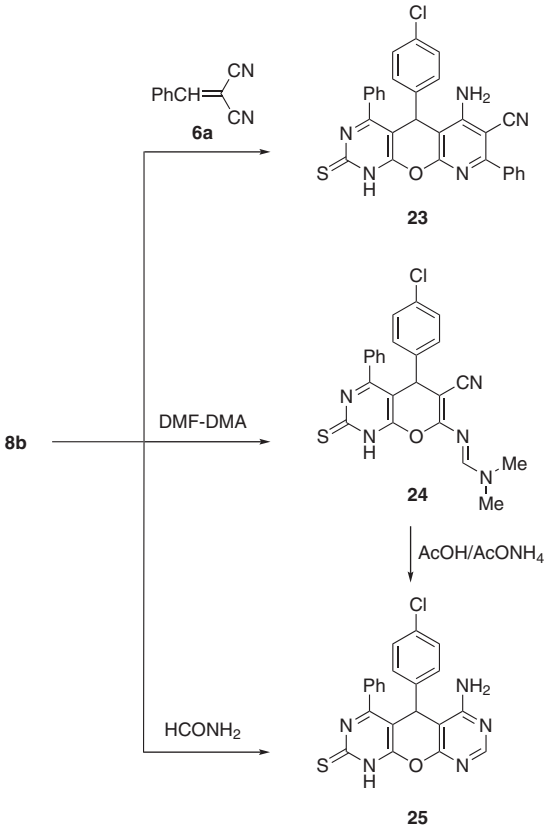
in the substrate **4** to the activated double bond in the unsaturated cyclohexanone followed by cyclization of the resultant intermediate adducts **17a–d.**

The utility of the pyranopyrimidines **8** in the synthesis of tricyclic fused heterocyclic compounds is illustrated in Schemes 4 and 5 by transformations of the selected compound **8b**. First, compound **8b** was allowed to react with chloroacetyl chloride in refluxing dioxane for 3 h to afford 2-chloroacetimide derivative **19**. A subsequent melting of compound **19** in the presence of ammonium acetate [28, 29] furnished the fused tricyclic product **22**. It can be suggested that the intermediate product **20** undergoes cyclization to **21,** which is transformed into the final product **22** by Dimroth rearrangement. However, the reaction of **8b** with chloroacetyl chloride in dioxane under reflux for 24 h gave the pyranopyrimidine **22** directly (Scheme 4).

Compound **8b** was also allowed to react with benzylidenemalononitrile **6a** in ethanol in the presence of a catalytic amount of piperidine under reflux to give the pyrido[3′,2′:5,6]pyrano[2,3-*d*]pyrimidine-7-carbonitrile **23** (Scheme 5). The formation of compound **23** is believed to involve an initial Michael addition of the amino function group in compound **8b** to the double bond of benzylidenemalononitrile followed by intramolecular cyclization of the resultant adduct. The infrared (IR), ^{1}H-nuclear magnetic resonance (^{1}H-NMR) and mass spectra of compound **23** fully support the proposed structure [26]. However, condensation of **8b** with dimethylformamide-dimethylacetal (DMF-DMA) yielded substituted formamidine **24.** Treatment of **24** with ammonium acetate in acetic acid



Scheme 4



Scheme 5

gave the tricyclic fused compound **25**. The same product **25** was obtained directly from **8b** by treatment with formamide. The structure of compound **25** was established by spectral analysis [30–32] (Scheme 5).

Conclusion

Compounds **4** and **8b** were used as starting materials for the efficient synthesis of new heterocyclic compounds.

Experimental

Melting points were determined using a Büchi apparatus and are uncorrected. IR spectra were recorded in KBr pellets on a Bruker-Vector 22 instrument. ^{1}H NMR spectra (300 MHz) and ^{13}C NMR spectra (75 MHz) were recorded on a Varian Gemini spectrometer with tetramethylsilane (TMS) as the internal reference. Electron impact (EI)-mass spectra were recorded on an HP D5988 A instrument. Elemental analyses were performed at the Microanalytical Centre at the Faculty of Science, Cairo University, Egypt.

General procedure for the preparation of compounds 4 and 5

A mixture of thiourea (0.76 g, 0.01 mol) and ethyl benzoylacetate (1.92 g, 0.01 mol) was stirred without solvent for 24 h at room temperature. The progress of the reaction was monitored by thin-layer chromatography (TLC). The solid mixture of **4** and **5** was filtered off, washed with diethyl ether, and separated by preparative TLC on silica gel 60 F-254 (Merk) eluting with toluene/acetone (10:4 v/v). Individual components were crystallized from ethanol. A mixture of **4** and **5** was used for the transformations described below.

6-Phenyl-2-thioxo-2,3-dihydropyrimidine-4(5*H*)-one (4) White crystals; yield 83%; mp 245–247°C; IR: 3207 (NH), 3076 (CH-arom), 1669 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 4.17 (s, 2H, CH_2), 7.02–7.57 (m, 6H, aromatic, and NH); 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.

6-Hydroxy-4-phenylpyrimidine-2(1*H*)-thione (5) Yellow crystals; yield 5%; mp 240–242°C; IR: 3380 (OH), 3275 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 6.07 (s, 1H, CH), 7.48–7.70 (m, 6H, aromatic, and NH), 12.49 (s, 1H, OH); ^{13}C NMR (DMSO-d_6): δ 179.3, 163.4, 154.6, 133.1,

131.02, 129.1, 129.1, 128.7, 128.7, 59.01; 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.

General procedure for the preparation of pyranopyrimidines 8a–e

A mixture of compound **4** (2.04 g; 0.01 mol) and arylidenemalononitrile **6a–e** (0.01 mol) in ethanol (50 mL) containing a catalytic amount of piperidine (0.25 mL) was heated under reflux for 12 h. The mixture was cooled, poured into crushed ice, and acidified with HCl. The separated solid of **8a–e** was filtered off, washed with water, and crystallized from ethanol.

7-Amino-4,5-diphenyl-2-thioxo-2,5-dihydro-1*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile (8a) White crystals; yield 82%; mp 108–110°C; IR: 3329, 3203 (NH_2), 3050 (CH-arom), 2934 (CH-aliph), 2185 (CN) cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.97 (s, 1H, 4H-pyrane), 6.13 (s, 2H, NH_2), 7.05–7.39 (m, 5H, aromatic), 7.42–7.79 (m, 5H, aromatic), 9.73 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 179.2, 162.9, 162.01, 159.1, 144.08, 133.2, 131.01, 129.1, 129.1, 128.6, 128.6, 128.5, 128.5, 127.6, 127.6, 125.6, 119.09, 75.01, 58.1, 34.7; 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 (8b) Yellow crystals; yield 84%; mp 186–188°C; IR: 3471, 3332 (NH_2), 3226 (NH), 2924 (CH), 2218 (CN) cm^{-1}; ^1H NMR (DMSO-*d6*): δ 5.02 (s, 1H, 4H-pyrane), 6.15 (s, 2H, NH_2), 7.00–7.29 (m, 4H, aromatic), 7.26–7.84 (m, 6H, aromatic, and NH); MS: *m/z* 393 ($M^+ + 1$). 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 (8c) Pale yellow crystals; yield 78%; mp 150–152°C; IR: 3336, 3200 (NH_2), 2936 (CH-aliph), 2191 (CN) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.38 (s, 1H, 4H-pyrane), 6.62 (s, 2H, NH_2), 6.95–7.49 (m, 4H, aromatic), 7.58–8.54 (m, 5H, aromatic), 9.28 (s, 1H, NH); 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 (8d) Green crystals; yield 70%; mp 180–182°C; IR: 3401, 3214 (NH_2), 2933 (CH-aliph), 2197 (CN) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.71 (s, 3H, OCH_3), 3.84 (s, 1H, 4H-pyrane), 7.061–7.088 (d, 2H, aromatic, $J = 8.1$ Hz), 7.437–7.464 (d, 2H, aromatic, $J = 8.1$ Hz), 7.30–7.85 (m, 8H, aromatic, NH, and NH_2); 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 (8e) Pale green crystals; yield 78%; mp 170–172°C; IR: 3349, 3228 (NH_2), 2932 (CH), 2193 (CN) cm^{-1}; ^1H 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, and NH); 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.

General procedure for the preparation of pyranopyrimidinethiones 12a–c

A mixture of compound **4** (2.04 g; 0.01 mol) and chalcone **10a–c** (0.01 mol) in ethanol (30 mL) containing a catalytic amount of piperidine (0.25 mL) was heated under reflux for 24 h. After cooling, the mixture was poured into crushed ice, and then acidified with HCl. The separated solid of **12a–c** was filtered off, washed with water, and crystallized from ethanol.

4,5,7-Triphenyl-1*H*-pyrano[2,3-*d*]pyrimidine-2(5*H*)-thione (12a) Pale yellow crystals; yield 88%; mp 100–102°C; IR: 3447 (NH), 2930 (CH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 5.12 (d, 1H, CH, $J = 7.8$ Hz), 5.39 (d, 1H, 4H-pyrane, $J = 5.1$ Hz), 6.78–7.51 (m, 5H, aromatic), 7.52–7.73 (m, 5H, aromatic), 7.92–8.53 (m, 5H, aromatic), 9.88 (s, 1H, NH); 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 (12b) Pale yellow crystals; yield 82%; mp 104–106°C; IR: 3444 (NH), 3063 (CH), 2922 (CH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 5.14 (d, 1H, CH, $J = 7.8$ Hz), 5.39 (d, 1H, 4H-pyrane, $J = 7.8$ Hz), 7.03–7.75 (m, 4H, aromatic), 7.85–8.16 (m, 5H, aromatic), 8.23–8.43 (m, 5H, aromatic), 10.00 (s, 1H, NH); 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 (12c) Pale yellow crystals; yield 72%; mp 98–100°C; IR: 3272 (NH), 3050 (CH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.84 (s, 3H, OCH_3), 5.33 (d, 1H, CH, $J = 4.8$ Hz), 5.38 (d, 1H, 4H-pyrane, $J = 4.8$ Hz), 6.97–7.04 (m, 4H, aromatic), 7.21–7.36 (m, 5H, aromatic), 7.64–8.70 (m, 5H, aromatic), 9.65 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 179.3, 162.9, 162.01, 157.5, 140.3, 136.1, 133.08, 131.01, 130.2, 130.02, 130.01, 129.2, 129.1, 128.7, 128.7, 128.5, 128.5, 127.7, 125.09, 125.09, 114.3, 114.1, 91.4, 75.02, 55.8, 37.3; 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.

7-Amino-4-phenyl-2-thioxo-2,5-dihydro-1*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile (14)

A mixture of dihydropyrimidinone derivative **4** (0.01 mol) and formaldehyde/malononitrile (0.01 mol) in ethanol (50 mL) containing a catalytic amount of piperidine (0.25 mL) was heated under reflux for 24 h. After cooling, the mixture was poured into crushed ice then acidified with HCl. The resultant solid product **14** was filtered off, washed with water, and crystallized from ethanol: Brown crystals; yield 73%; mp 258–260°C; IR: 3330, 3180 (NH_2), 2926 (CH), 2203 (CN) cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.12 (s, 2H, CH_2), 6.01 (s, 2H, NH_2), 7.21–7.91 (m, 5H, aromatic), 12.00 (hump, 1H, NH); 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.

General procedure for the preparation of carbonitriles 16a,b

A mixture of compound **4** (0.01 mol), 2-(ethoxymethylene)malononitrile (0.01 mol) or ethyl 2-cyano-3-ethoxyacrylate (0.01 mol) in ethanol (50 mL) containing a catalytic amount of piperidine (0.25 mL) was heated under reflux for 24 h. The mixture was cooled, poured into crushed ice, and acidified with HCl. The resultant solid of **16a,b** was filtered off, washed with water, and crystallized from ethanol.

7-Imino-4-phenyl-2-thioxo-2,7-dihydro-1*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile (16a)

Brown crystals; yield 78%; mp 288–290°C; IR: 3420, 3339 (2NH), 2924 (CH), 2210 (CN) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.25–8.20 (m, 7H), 13.80 (s, 1H, NH); 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-dihydro-1*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile (16b)

Yellow crystals; yield 83%; mp 108–110°C; IR: 3333 (NH), 2932 (CH), 2214 (CN), 1689 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.26–8.18 (m, 6H), 13.80 (s, 1H, NH); 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.

General procedure for the preparation of chromenopyrimidinethiones 18a–d

A mixture of compound **4** (2.04 g; 0.01 mol) and 2-(benzylidene) cyclohexanone (0.01 mol) in ethanol (30 mL) containing a catalytic amount of piperidine (0.25 mL) was heated under reflux for 24 h. After cooling, the mixture was poured into crushed ice and acidified with HCl. The separated solid of **18a–d** was filtered, washed with water, and crystallized from ethanol.

4,5-Diphenyl-6,7,8,9-tetrahydro-1*H*-chromeno[2,3-*d*]pyrimidine-2(5*H*)-thione (18a) Pale yellow crystals; yield 84%; mp 105–107°C; IR: 3420 (NH), 3056 (CH), 2932 (CH) cm^{-1}; ^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), 6.95–7.22 (m, 5H, aromatic), 7.32–7.56 (m, 5H, aromatic), 7.81 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 179.3, 162.9, 162.07, 144.08, 142.3, 133.1, 131.07, 129.1, 129.1, 128.7, 128.7, 128.5, 128.5, 127.6, 127.6, 125.7, 110.9, 75.0, 29.6, 26.1, 23.8, 23.4, 22.6; 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 (18b) Pale yellow crystals; yield 86%; mp 111–113°C; IR: 3434 (NH), 3050 (CH), 2923 (CH) cm^{-1}; ^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), 6.67–7.01 (m, 4H, aromatic), 7.26–8.01 (m, 5H, aromatic); 9.35 (s, 1H, NH); 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 (18c) Yellow crystals; yield 81%; mp 140–142°C; IR: 3381 (NH), 2938 (CH) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.79–2.18 (m, 4H, $2CH_2$), 2.92 (m, 4H, $2CH_2$), 3.85 (s, 3H, OCH_3), 3.89 (s, 1H, 4H-pyrane), 6.94 (d, 2H, aromatic, *J* = 8.4 Hz), 7.47 (d, 2H, aromatic, *J* = 8.4 Hz), 7.26–7.78 (m, 6H, aromatic, and NH); 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*]pyrimidine-2(5*H*)-thione (18d) Pale yellow crystals; yield 80%; mp 102–104°C; IR: 3339 (NH), 3060 (CH), 2932 (CH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.88–1.56 (m, 4H, $2CH_2$), 1.90–2.40 (m, 4H, $2CH_2$), 3.79 (s, 1H, 4H-pyrane), 6.65–7.12 (m, 4H, aromatic), 7.14–7.42 (m, 5H, aromatic), 8.25 (s, 1H, NH), 9.12 (s, 1H, OH); 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.

Synthesis of 2-chloro-*N*-(5-(4-chlorophenyl)-6-cyano-4-phenyl-2-thioxo-2,5-dihydro-1*H*-pyrano[2,3-*d*]pyrimidine-7-yl)acetamide (19)

A mixture of **8b** (0.01 mol) and 2-chloroacetyl chloride (0.01 mol) in dioxane (30 mL) was heated under reflux for 3 h. The mixture was cooled and the separated solid of **19** was filtered, washed with cold ethanol, and crystallized from ethanol: Pale yellow crystals; yield 80%; mp 100–102°C; IR: 3330, 3212 (2NH), 3065 (CH), 2956 (CH), 2214 (CN), 1731 (CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.31 (s, 2H, CH_2), 5.23 (s, 1H, 4H-pyrane), 6.94–7.52 (m, 4H, aromatic), 7.54–8.29 (m, 5H, aromatic), 10.17 (s, 1H, NH), 11.76 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 179.3, 162.9, 164.6, 162.01, 151.09, 142.4, 133.3, 131.2, 131.01, 130.3, 129.1, 128.9, 128.7, 119.1, 75.02, 60.2, 44.8, 34.5; 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.

Synthesis of 8-(chloromethyl)-5-(4-chlorophenyl)-4-phenyl-2-thioxo-5,7-dihydro-1*H*-pyrano[2,3-d:6,5-*d*′]dipyrimidine-6(2*H*)-one (22)

Method A A mixture of **8b** (0.01 mol) and 2-chloroacetyl chloride (0.01 mol) in dioxane (50 mL) was heated under reflux for 24 h. After cooling, the separated solid of **22** was filtered, washed with cold ethanol, and crystallized from ethanol.

Method B A mixture of **19** (0.01 mol) and ammonium acetate was fused for 6 h. After cooling and trituration with cold ethanol, the solid product **22** was filtered off, washed with water, and crystallized from ethanol.

Compound **22** was obtained in 71% yield (method A) and 70% yield (method B): Pale yellow crystals; yield; mp 320–322°C; IR: 3143 (NH), 3045 (CH), 2807 (CH), 1660 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.18 (s, 1H, NH), 3.50 (s, 2H, CH_2), 3.77 (s, 1H, 4H-pyrane), 7.17–7.27 (m, 4H, aromatic), 7.36–7.61 (m, 6H, aromatic, and NH); ^{13}C NMR ($CDCl_3$): δ 179.3,

162.9, 164.03, 162.1, 162.02, 161.9, 142.5, 133.1, 131.2, 131.01, 130.3, 129.1, 128.9, 128.7, 100.7, 75.0, 49.5, 36.0; 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.

Synthesis of 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 (23)

A mixture of **8b** (3.92 g; 0.01 mol) and 2-(benzylidene)malononitrile **(6a**, 0.01 mol) in ethanol (50 mL) containing a catalytic amount of piperidine (0.25 mL) was heated under reflux for 8 h. After cooling, the mixture was poured into crushed ice and acidified with HCl. The separated solid of **23** was filtered, washed with water, and crystallized from ethanol: Pale yellow crystals; yield 77%; mp 110–112°C; IR: 3331, 3203 (NH_2), 3087 (CH), 2933 (CH), 2190 (CN) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.06 (s, 1H, 4H-pyrane), 6.19 (s, 2H, NH_2), 7.31–7.50 (m, 4H, aromatic), 7.52–7.79 (m, 5H, aromatic), 7.80–7.96 (m, 5H, aromatic), 9.31 (s, 1H, NH); 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.

Synthesis of *N′*-(5-(4-chlorophenyl)-6-cyano-4-phenyl-2-thioxo-2,5-dihydro-1*H*-pyrano[2,3-*d*]pyrimidine-7-yl)-*N,N*-dimethylformimidamide (24)

A mixture of (**8b**, 0.01 mol) and DMF-DMA (0.01 mol) in xylene (30 mL) was heated under reflux for 6 h. After cooling, the separated solid of **24** was filtered, washed with cold ethanol, and crystallized from ethanol: Brown crystals; yield 81%; mp 210–212°C; IR: 3340 (NH), 2926 (CH), 2210 (CN) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.28 (s, 6H, $2CH_3$), 4.27 (s, 1H, 4H-pyrane), 7.36–7.40 (m, 4H, aromatic), 7.42–7.61 (m, 7H, aromatic, N=CH, and NH); 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.

Synthesis of 6-amino-5-(4-chlorophenyl)-4-phenyl-1,5-dihydro-2*H*-pyrimido[5′,4′:5,6]pyrano[2,3-*d*]pyrimidine-2-thione (25)

Method A A mixture of **8b** (0.01 mol) and formamide (0.01 mol) in xylene (30 mL) was heated under reflux for 24 h, then cooled, and poured into crushed ice. The separated solid of **25** was filtered, washed with water, and crystallized from ethanol.

Method B A mixture of **24** (0.01 mol), AcOH and $AcONH_4$ was heated under reflux for 12 h, then cooled, poured into crushed ice, and acidified with HCl. The separated solid of **25** was filtered, washed with water, and crystallized from ethanol: Yield 79% (method A) and 70% (method B); mp 150–152°C; IR: 3460, 3440 (NH_2), 3202 (NH), 2902 (CH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.10 (s, 1H, 4H-pyrane), 6.04 (s, 2H, NH_2), 6.72 (s, 1H, pyrimidine), 6.99–7.31 (m, 4H, aromatic), 7.36–8.86 (m, 6H, aromatic, and NH); MS: *m/z* 421 ($M^+ + 2$). Anal. Calcd for $C_{21}H_{14}ClN_5OS$ (419): 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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