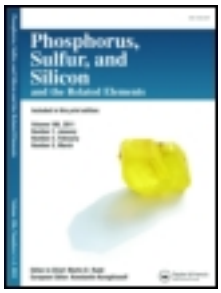

Phosphorus, Sulfur, and Silicon and the Related Elements

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Synthesis of Some New Thiazolo[3,2- a]pyrido[2,3- d]pyrimidinones and Isoxazolo[5′,4′:4,5]thiazolo [3,2- a]pyrido[2,3- d]pyrimidinone

A. B. A. El-Gazzar [a] , A. M. Gaafar [a] & A. S. Aly [a]

[a] National Research Centre, Cairo, Egypt

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SYNTHESIS OF SOME NEW THIAZOLO[3,2-*a*]PYRIDO[2,3-*d*]PYRIMIDINONES AND ISOXAZOLO[5′,4′:4,5]THIAZOLO [3,2-*a*]PYRIDO[2,3-*d*]PYRIMIDINONE

A. B. A. El-Gazzar, A. M. Gaafar, and A. S. Aly*
National Research Centre, Cairo, Egypt

(Received April 24 2001.)

*6-Amino-2,3-dihydro-2-thioxo-4(1*H*)-pyrimidinone* ***1*** *reacts in boiling DMF with a cyclic α,β-unsaturated ketones* ***2*** *affording the pyrido [2,3-*d*]pyrimidinone* ***6a,b****, the latter compound condensed with aldehyde in presence of chloroacetic acid to yield thiazolo[3,2-a] pyrido [2,3-d]-pyrimidinones (****7****,* ***8****) respectively. The alkylation of pyrido-pyrimidinone it gave the 2-alkylthio derivatives* ***10a–e****, compound* ***10b*** *cyclized to thiazolopyridopyrimidinone derivative* ***13****. Also, the condensation of compounds* ***7a,b*** *with hydoxylamine gave the corresponding isoxazolo[5′,4′:4,5]thiazolo[3,2-a]pyrido[2,3-d]pyrimidinone.*

Keywords: 6-Aminothiouracil; α,β-unsaturated ketones; spectroscopic analysis (NMR, mass)

It is well known that among pyrimidinone (6-amino uracil) derivatives and their nucleosides, there are many compounds containing a fused pyrimidine ring. These make up a broad class owing to the wide range of biological activity. Many potential drugs have been modelled on these compounds, particularly in cancer and virus research.[1]

On the other hand, pyrido[2,3-*d*]pyrimidines and their oxo and thioxo derivatives deserve great interest by virtue of their biological and physiological properties.[2–16] Thus, in connection with our recent work,[17–19] we report a new approach to some novel thiazolo [3,2-*a*]pyrido[2,3-*d*]pyrimidinone and isoxazolo[5′,4′:4,5]thiazolo[3,2-*a*] pyrido[2,3-*d*]pyrimidinone derivatives utilizing readily available starting materials.

According to Skrap and Doebner-v. Miller[20,21] synthesis of pyridines, the reaction of 6-amino-2-thiouracil and α,β-unsaturated ketones is

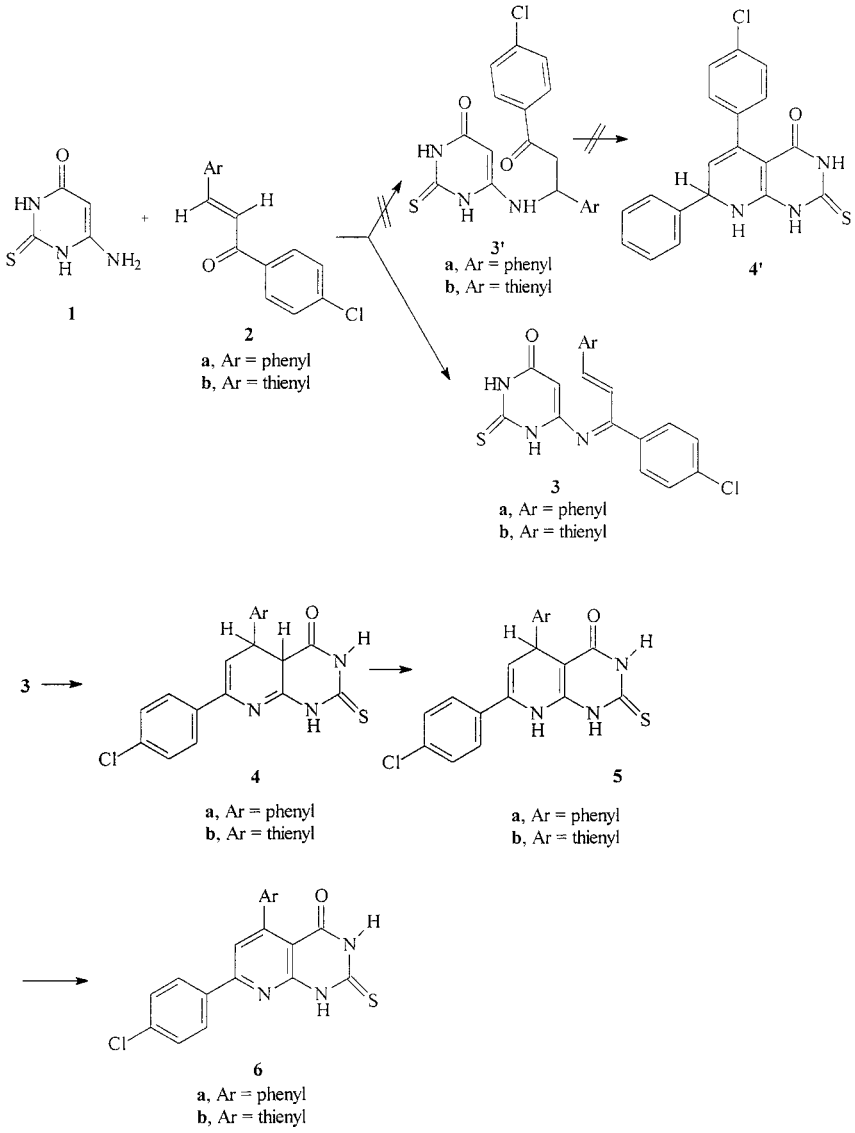
Address correspondence to A. B. A. El-Gazzar, National Research Center, Cairo, Egypt.

a very convenient and versatile method for the fusion of a pyridine ring to the pyrimidinone as a heterocycle ring.[22–25] Where, the neucleophilic amine **1** can attack on the carbonyl carbon C-1 or on C-3 of the ketones **2**,[26] the formation of **3** or **3′** not only depends on the educts but also on the reaction condition.[27] Thus, 6-amino thiouracil **1**,[28] condensed with α,β-unsaturated ketones **2** forming the 5,7-diaryl-2,3,5,8-tetrahydro-2-thioxopyrido[2,3-*d*]pyrimidin-4(1*H*)-ones **4** or **4′**. Actually, only one reaction route is realized. Depending on the reaction conditions, the compounds **5** or **6** were isolated. Boiling of **3** in DMF in an argon atmosphere leads to **5**, an energetically favorable tautomer of **4**,[26] (Scheme 1).

However, we reported here, that the prolonged reaction for compounds **5** are smoothly oxidized to **6** in boiling DMF in presence of air, with yield 85%, respectively. Also, the structure form of the oxidized product **6** was investigated by NMR spectrum and elemental analysis, where the low field shift for the protons of the aryl group linked to C-5 is due to the anisotropy effect of the pyrido[2,3-*d*]pyrimidine skeleton, particularly of its carbonyl group.

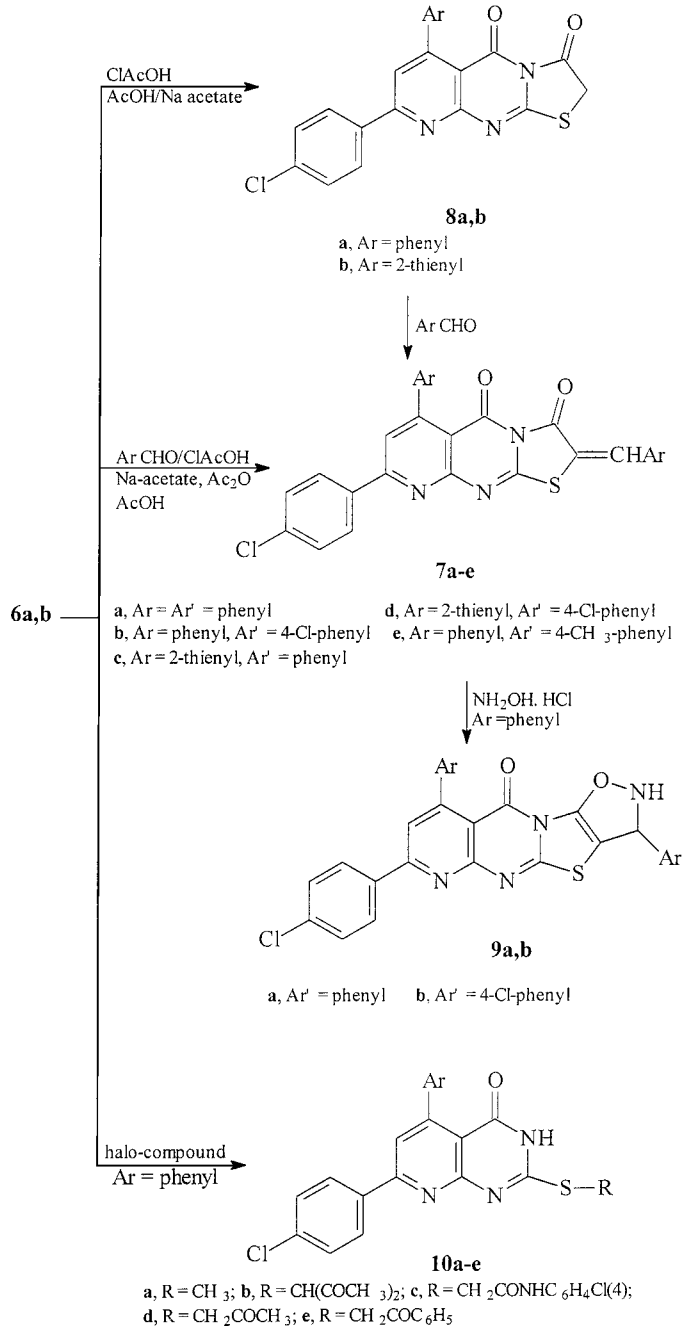
Also, we can investigated the reaction of **1** and 3-(4-chlorophenyl)-1-(2-theinyl)-2-propen-1-one (**2b**) as α,β-unsaturated ketone containing a heterocycle ring, yielding 5-(2-theinyl)pyrido[2,3-*d*]pyrimidinone (**6b**), respectively. Its NMR showed signals at δ 7.23 (t, 1H, thienyl proton), 7.40 (d, 1H, thienyl proton), 7.45–7.60 (d, 2H), 7.73 (d, 1H, thienyl proton), 7.97 (s, 1H, pyridine proton), 8.28 (d, 2H), 12.15, 13.00 (two, br, s, 2NH, D_2O exchangable), which were identical with the structure form. Also, MS showed the molecular ion peak (M^+) 371, 100%. (See Experimental Section and Scheme 1).

As mentioned before, the development of the syntheses of various derivatives of pyrido[2,3-*d*]pyrimidines and fused pyrimidines was promoted to us. Thus, when a ternary mixture of compound **6a**,**b**, chloroacetic acid, and a proper aldehyde was heated under reflux in a mixture of acetic acid, acetic anhydride, in the presence of anhydrous sodium acetate, 8-(4-chlorophenyl)-6-phenyl (or 2-theinyl)-2-arylmethylene-2,3,4,5-tetrahydrothiazolo [3,2-*a*]pyrido[2,3-*d*]pyrimidine-3,5-dione (**7a–e**). Assignment of structure **7** to the reaction products is based on correct values of elemental analysis and compatible spectral data. Mass spectrum showed [M^+], *m/z* 507 (100%) as a molecular ion peak for compound **7e** as an example. Also, the condensation of 2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrido[2,3-*d*]pyrimidine-3,5-dione (**8a**) with benzaldehyde in acetic acid and anhydrous sodium acetate under reflux afforded a similar reaction to product **7a**, with identical data (see Experimental Section; Scheme 2).



SCHEME 1

Compounds **7a**,**b** underwent cycloaddition with hydroxyl amine hydrochloride, by refluxing in acetic acid in the presence of anhydrous sodium acetate to give 3-aryl-7-(4-chlorophenyl)-9-phenyl-2,3-dihydro isoxazolo[5′,4′:4,5]thiazolo[3,2-*a*]pyrimido[2,3-*d*]pyrimidin-10(10*H*)-ones (**9a**,**b**). The ^{1}H NMR spectrum (DMSO-d_6) of **9a** as an example, showed signals at δ 6.45 (s, 1H, isoxazole proton), 7.03–7.50 (m, 10H,



SCHEME 2

two phenyl proton), 7.55 (d, 2H), 7.95 (s, 1H, pyridine proton), 8.25 (d, 2H), 11.25 (br, s, NH, D_2O exchangeable). The IR spectra of **9a** displayed absorption bands around 3290 cm^{-1} (NH) and 1688 cm^{-1} for the amidic carbonyl group (see Experimental Section; Scheme 2).

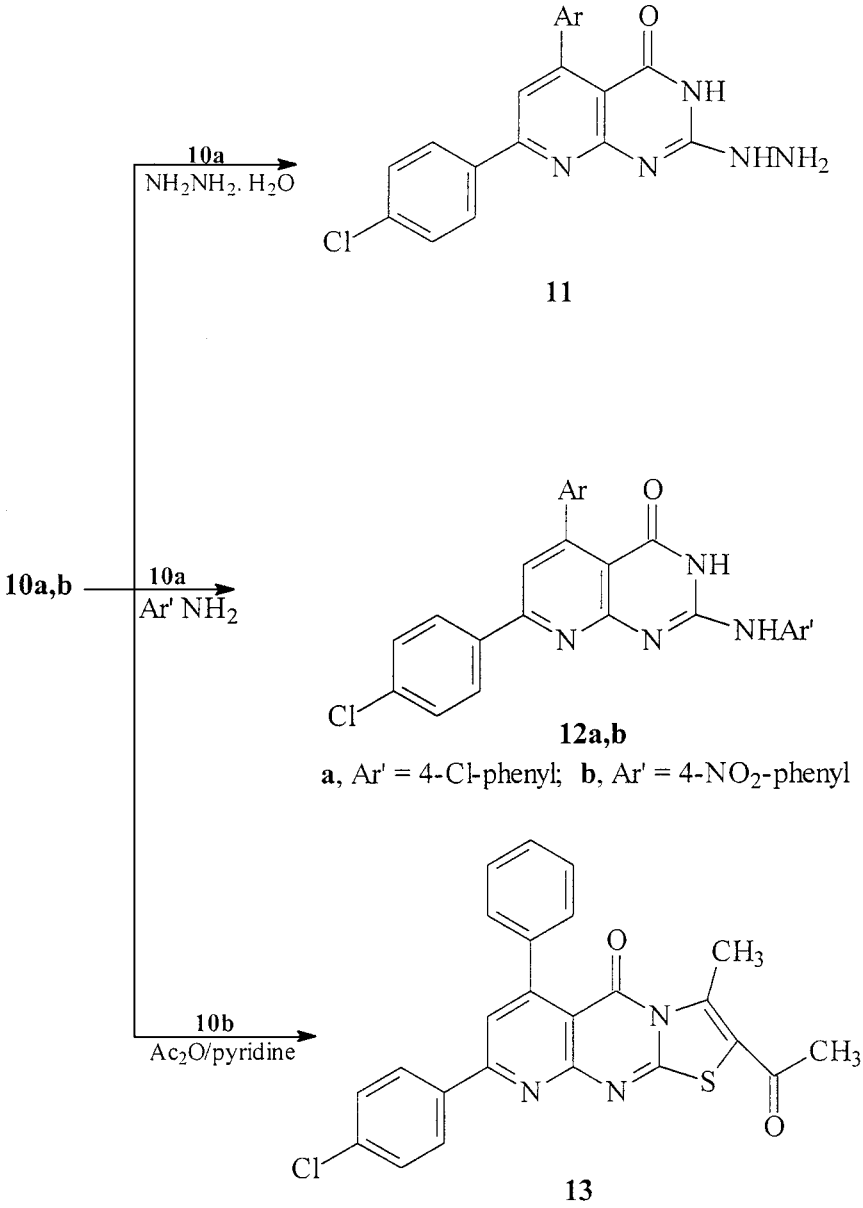
Alkylation of **6a** in an ethanolic potassium hydroxide solution with a proper halogeno compounds, mainly, methyl iodide, chloroacetyl acetone, 2-chloro aceto(4-chlorophenyl)anilide, chloroacetone and phenacyl bromide, yielded the 2-alkylthio derivatives **10a–e**, respectively. Assignment of structure **10** to the reaction products is based on the fact that each of **10a**,**b** gave the same 2-hydrazino derivatives **11** when refluxed with hydrazine hydrate in dioxane. Also, ^{1}H NMR and mass spectronomy showed reasonable data, (Scheme 3). Also, when compound **10a** was fused with anilines derivatives mainly, 4-chloroaniline and 4-nitroaniline at 140°C, it gave 2-aryl amino derivatives **12a**,**b**, respectively. The structure was confirmed by elemental analysis, and spectral data (Scheme 3).

Furthermore, heating under reflux compound **10b**, in a mixture of acetic anhydride/pyridine (1:1), led to cyclization and formation of 2-acetyl-8-(4-chlorophenyl)-3-methyl-6-phenyl-5*H*-thiazolo[3,2-*a*]pyrido[2,3-*d*]pyrimidin-5-one (**13**), (Scheme 3). Structural elucidation of compound **13** was accomplished from analytical and spectral data. The mass spectra showed the expected molecular ion peak (*m/z* 445, 100%) and the IR spectra displayed two carbonyl absorption bands at 1729 and 1689 cm^{-1} and no signals for NH. Also, the ^{1}H NMR spectrum (DMSO-d_6) showed signals at δ 2.60 (s, 3H), 2.85 (s, 3H), 7.35–7.50 (m, 5H, phenyl), 7.60, 8.30 two doublet signals for 4-chlorophenyl, and 7.80 ppm (s, CH, pyridine proton attached to C-7).

In conclusion, pyrido[2,3-*d*]pyrimidinones, which are easily prepared by the cycloaddition of α,β-unsaturated ketones to 6-amino thiouracil, were found to be useful starting materials for the synthesis of thiazolo[3,2-*a*]pyridino[2,3-*d*]pyrimidinone derivatives. The advantage of this method over the other existing methods is that pyrido[2,3-*d*] pyrimidinones are obtained in the oxidized form in quantitative yields, and further reaction with hydroxyl amine, aromatic amines, and halocompounds produce excellent yields of 2-alkylthio, thiazolo, isoxazolo thiazolo pyridopyrimidinones. No other side products are obtained.

EXPERIMENTAL

All melting points are uncorrected, the NMR spectra were recorded on a Varian ^{1}H Gemini 200 spectrometer (NRC) and chemical shifts were expressed as δ values against $SiMe_4$ as internal standards. IR spectra



SCHEME 3

were recorded as KBr pellets on a Perkin-Elmer 1430 spectrometer, (National Research Centre and Department of Chemistry, Cairo University). Mass spectra were recorded on GCMS-QP 1000Ex Shimadzu Japan (Gas Chromatography-Mass Spectrometer). Microanalyses data were performed by the Microanalytical Centre at Cairo University and National Research Centre.

7-(4-Chlorophenyl)-2,3-dihydro-5-Phenyl or (2-theinyl)-2-thioxopyrido[2,3-d]pyrimidin-4(1H)-one (6a,b)

General Procedure

A mixture from compound **1** (10 mmol) and α,β-unsaturated ketones **2** (10 mmol) was refluxed in DMF (50 ml) for 30 h (under TLC control). The mixture was cooled, and the percipitate was filtered off and crystallized from appropriate solvent to produce (**6a**,**b**), respectively.

*7-(4-Chlorophenyl)-2,3-dihydro-5-phenyl-2-thioxopyrido[2,3-d]pyrimidin-4(1H)-one (**6a**).* From compound **1** (1.43 g, 10 mmol) and **2a** (2.43 g, 10 mmol). The compound was obtained as a yellow crystals, crystallized from DMF, m.p. 344–346°C (dec.) in 88% yield; ($C_{19}H_{12}ClN_3OS$) (365.8). IR (KBr) cm^{-1}: 3219 (NH), 1678 (C=O), 1663 (C=N); ^1H NMR (DMSO-d_6) ppm: δ 7.45–7.60 (m, 5H, phenyl), 7.65 (d, 2H), 7.95 (s, 1H, pyridine proton), 8.25 (d, 2H), 12.40, 13.10 (two br, s, NH, D_2O exchangeable). Mass: (70 ev) *m/z* (%) 365 (M^+, Cl^{35}, 100), 367 (M^+, Cl^{37}, 30).

*7-(4-Chlorophenyl)-2,3-dihydro-5-(2-theinyl)-2-thioxopyrido[2,3-d]-pyrimidin-4(1H)-one (**6b**).* From compound **1** (1.43 g, 10 mmol) and **2b** (2.49 g, 10 mmol). The compound was obtained as a yellow crystals, crystallized from DMF, m.p. 328–330°C (dec.) in 78% yield; ($C_{17}H_{10}ClN_3OS_2$) (371.8). IR (KBr) cm^{-1}: 3306 (NH), 1683 (C=O), 1661 (C=N); ^1H NMR (DMSO-d_6) ppm: δ 7.23 (t, 1H, thienyl proton), 7.40 (d, 1H, thienyl proton), 7.45–7.60, 8.28 (two, d, 4H, 4-chlorophenyl), 7.73 (d, 1H, thienyl proton), 7.97 (s, 1H, pyridine proton), 12.15, 13.00 (two br, s, NH, D_2O exchangeable).

8-(4-Chlorophenyl)-6-Aryl-2-arylmethylene-2,3,4,5-tetrahydrothiazolo[3,2-a]pyrido[2,3-d]pyrimidine-3,5-Dione (7a–e)

General Procedure

Method A: A mixture of compound **6** (10 mmol), the appropriate aromatic aldehyde (10 mmol), and (1.64 g, 20 mmol) of anhydrous sodium acetate was stirred under reflux in glacial acetic acid (30 ml) and acetic anhydride (15 ml) for 2 h. The reaction mixture was allowed to cool to

room temperature and poured into cold water (100 ml). The deposited precipitate was filtered off, and crystallized from appropriate solvent to produce **7a–e**.

Method B: A mixture of compound **8a** (4.06 g, 10 mmol), benzaldehyde (1.06 g, 10 mmol), and (1.64 g, 20 mmol) of anhydrous sodium acetate was stirred under reflux in glacial acetic acid (30 ml) and acetic anhydride (15 ml) for 3 h. The reaction mixture was allowed to cool to room temperature and poured into cold water (100 ml). The deposited precipitate was filtered off and crystallized from DMF to produced **7a**.

*8-(4-Chlorophenyl)-6-phenyl-2-phenylmethylene-2,3,4,5-tetrahydrothiazolo[3,2-a]pyrido[2,3-d]pyrimidine-3,5-dione (**7a**).* From compound **6a** (3.66 g, 10 mmol) and benzaldehyde (1.06 g, 10 mmol). The compound was obtained as a yellow powder, crystallized from dioxane/DMF (1:1); m.p. 273–275°C (dec.) in 68% yield; ($C_{28}H_{16}ClN_3O_2S$) (493.9). IR (KBr) cm^{-1}: 1681, 1678 (2 C=O), 1662 (C=N); ^1H NMR (DMSO-d_6) ppm: δ 7.38–7.65 (m, 10H, two phenyl protons), 7.71 (d, 2H), 7.80 (s, 1H, methylenic proton), 7.98 (s, 1H, pyridine proton), 8.31 (d, 2H).

*8-(4-Chlorophenyl)-2-(4-chlorophenyl methylene)-6-phenyl-2, 3, 4, 5-tetrahydrothiazolo[3,2-a]pyrido[2,3-d]pyrimidine-3,5-dione (**7b**).* From compound **6a** (3.66 g, 10 mmol) and 4-chlorobenzaldehyde (1.41 g, 10 mmol). The compound was obtained as a yellow powder, crystallized from DMF; m.p. 332–335°C (dec.) in 71% yield; ($C_{28}H_{15}Cl_2N_3O_2S$) (528.4). IR (KBr) cm^{-1}: 1693, 1684 (2 C=O), 1661 (C=N); ^1H NMR (DMSO-d_6) ppm: δ 7.40–7.55 (m, 5H, phenyl proton), 7.65–7.70 (two, d, 4H), 7.78 (s, 1H, methylenic proton), 7.97 (s, 1H, pyridine proton), 8.25–8.35 (two, d, 4H).

*8-(4-Chlorophenyl)-2-phenylmethylene-6-(2-thienyl)-2,3,4,5-tetrahydrothiazolo[3,2-a]pyrido[2,3-d]pyrimidine-3,5-dione (**7c**).* From compound **6b** (3.72 g, 10 mmol) and benzaldehyde (1.06 g, 10 mmol). The compound was obtained as a pale yellow crystals, crystallized from dioxane/DMF (1:1); m.p. 293–295°C (dec.) in 56% yield; ($C_{26}H_{14}ClN_3O_2S_2$) (499.9). IR (KBr) cm^{-1}: 1691, 1685 (2 C=O), 1659 (C=N); ^1H NMR (DMSO-d_6) ppm: δ 7.21 (t, 1H, thienyl proton), 7.40–7.56 (m, 6H, 5H phenyl + 1H thienyl), 7.63 (d, 2H), 7.71 (d, 1H, thienyl proton), 7.73 (s, 1H, methylenic proton), 7.96 (s, 1H, pyridine proton), 8.26 (d, 2H).

*8-(4-Chlorophenyl)-2-(4-chlorophenylmethylene)-6-(2-thienyl)-2,3,4, 5-tetrahydrothiazolo[3,2-a]pyrido[2,3-d]pyrimidine-3,5-dione (**7d**).* From compound **6b** (3.72 g, 10 mmol) and 4-chlorobenzaldehyde (1.41 g, 10 mmol). The compound was obtained as a yellow powder, crystallized from DMF; m.p. 318–321°C (dec.) in 63% yield;

($C_{26}H_{13}Cl_2N_3O_2S_2$) (534.4). IR (KBr) cm^{-1}: 1689, 1681 (2 C=O), 1654 (C=N); ^1H NMR (DMSO-d_6) ppm: δ 7.22 (t, 1H, thienyl proton), 7.42 (d, 1H, thienyl proton), 7.58–7.63 (two, d, 4H), 7.72, (d, 1H, thienyl proton), 7.79 (s, 1H, methylenic proton), 7.95 (s, 1H, pyridine proton), 8.21 (d, 2H), 8.28 (d, 2H).

*8-(4-Chlorophenyl)-2-(4-tolyl)-6-phenyl-2,3,4,5-tetrahydrothiazolo[3, 2-a]pyrido[2,3-d]pyrimidine-3,5-dione (**7e**).* From compound **6a** (3.66 g, 10 mmol) and 4-methylbenzaldehyde (1.20 g, 10 mmol). The compound was obtained as a yellow crystals, crystallized from DMF; m.p. 328–330°C (dec.) in 81% yield; ($C_{29}H_{18}ClN_3O_2S$) (507.9). IR (KBr) cm^{-1}: 1695, 1688 (2 C=O), 1667 (C=N); ^1H NMR (DMSO-d_6) ppm: δ 2.65 (s, 3H, CH_3), 7.38–7.52 (m, 7H, 5 phenyl proton + 2H(4-sub)), 7.62 (d, 2H), 7.69 (s, 1H, methylenic proton), 7.93 (s, 1H, pyridine proton), 8.09 (d, 2H), 8.28 (d, 2H); Mass (70 ev) *m/z* (%): 507.2 (M^+, Cl^{35}, 100), 509.2 (M^+, Cl^{37}, 29.8), 478 (7), 365 (10), 332 (46).

8-(4-Chlorophenyl)-2,3-dihydro-6-phenyl or (2-thienyl)-5H-thiazolo[3,2-a]pyrido[2,3-d]pyrimidine-3,5-dione (8a,b)

General Procedure

A mixture of compound **6a,b** (10 mmol), chloroacetic acid (0.95 g, 10 mmol), and (1.64 g, 20 mmol) anhydrous acetate was gently heated with stirring on a waterbath (60°C) for 2 h. The reaction mixture was allowed to cool to room temperature and poured into water (100 ml). The deposited precipitate was filtered off and crystallized from dioxane to produce **8a**,**b** respectively.

*8-(4-Chlorophenyl)-2,3-dihydro-6-phenyl-5H-thiazolo[3,2-a]pyrido-[2,3-d] pyrimidine-3,5-dione (**8a**).* From compound **6a** (3.66 g, 10 mmol). The compound was produced as a white powder, crystallized from dioxane in 49%; m.p. 214–216°C (dec.); ($C_{21}H_{12}ClN_3O_2S$) (405.8). IR (KBr) cm^{-1}: 1703, 1689 (2 C=O), 1668 (C=N); ^1H NMR (DMSO-d_6) ppm: δ 3.62 (s, 2H, CH_2), 7.40–7.50 (m, 5H, phenyl proton), 7.60 (d, 2H), 7.95 (s, 1H, pyridine proton), 8.30 (d, 2H).

*8-(4-Chlorophenyl)-2,3-dihydro-6-(2-thienyl)-5H-thiazolo[3,2-a]pyrido[2,3-d]pyrimidine-3,5-dione (**8b**).* From compound **6b** (3.72 g, 10 mmol). The compound was produced as a yellow crystals, crystallized from dioxane in 47%; m.p. 239–241°C (dec.); ($C_{19}H_{10}ClN_3O_2S_2$) (411.8). IR (KBr) cm^{-1}: 1708, 1689 (2 C=O), 1658 (C=N); ^1H NMR (DMSO-d_6) ppm: δ 3.63 (s, 2H, CH_2), 7.21 (t, 1H, thienyl proton), 7.41

(d, 1H, thienyl proton), 7.65 (d, 2H), 7.72 (d, 1H, thienyl proton), 7.98 (s, 1H, pyridine proton), 8.27 (d, 2H).

7-(4-Chlorophenyl)-3-phenyl or (4-chlorophenyl)-9-phenyl-2,3-dihy-dro-isoxazolo[5′,4′: 4,5]thiazolo-[3,2-a]pyrido[2,3-d]pyrimidin-10(10H)-one (9a,b)

General Procedure

A mixture of compound **7a**,**b** (10 mmol), hydroxylamine hydrochloride (0.70 g, 10 mmol) and (1.64 g, 20 mmol) anhydrous acetate was stirred under reflux in glacial acetic acid (30 ml) for 5 h. The reaction mixture was allowed to cool to room temperature and poured into cold water (100 ml). The deposited precipitate was filtered off, dried, and crystallized from appropriate solvent to produce **9a**,**b**.

*7-(4-Chlorophenyl)-3,9-diphenyl-2,3-dihydroisoxazolo[5′,4′:4,5]-thiazolo[3,2-a]pyrido[2,3-d]pyrimidin-10(10H)-one (**9a**).* From compound **7a** (4.94 g, 10 mmol). The compound was produced as a colorless crystals, crystallized from benzene in 61% yield; m.p. 317–319°C (dec.); ($C_{28}H_{17}ClN_4O_2S$) (508.9). IR (KBr) cm^{-1}: 3219 (NH), 1689 (C=O), 1659 (C=N); ^1H NMR (DMSO-d_6) ppm: δ 6.45 (s, 1H, isoxazoloproton), 7.30–7.50 (m, 10H, two phenyl proton), 7.58 (d, 2H), 7.94 (s, 1H, pyridine proton), 8.25 (d, 2H), 11.25 (br, s, NH).

*3,7-Di(4-chlorophenyl)-9-phenyl-2,3-dihydroisoxazolo[5′,4′:4,5]-thiazolo [3, 2-a]pyrido[2, 3-d] pyrimidin-10 (10H)-one (**9b**).* From compound **7b** (5.28 g, 10 mmol). The compound was produced as a colorless crystals, crystallized from cyclohexane in 58% yield; m.p. 307–309°C (dec.); ($C_{28}H_{16}Cl_2N_4O_2S$) (543.4). IR (KBr) cm^{-1}: 3228 (NH), 1686 (C=O), 1653 (C=N); ^1H NMR (DMSO-d_6) ppm: δ 6.42 (s, 1H, isoxazole proton), 7.32–7.50 (m, 5H, phenyl), 7.61 (two, d, 4H), 7.97 (s, 1H, pyridine proton), 8.11 (d, 2H), 8.27 (d, 2H), 10.58 (br, s, NH).

2-(S-Alkyl)-5-Phenyl-7-(4-Chlorophenyl)-3H,4H-pyrido[2, 3-d]-pyrimidin-4-one (10a–e)

General Procedure

To a warmed ethanolic potassium hydroxide solution (prepared by dissolving 0.56 g, 10 mmol of potassium hydroxide in 50 ml ethanol) was added each of compound **6a** (3.66 g, 10 mmol), the heating was continued for 30 min, then the mixture was allowed to cool to room temperature and the proper halo-compound (10–12 mmol) was added. The mixture was stirred under reflux for 5 h, then cool to room temperature and poured into cold water (100 ml). The solid produced so-precipitated was filtered off and washed with (100 ml) water; the product was

dried and crystallized from appropriate solvent to produce (**10a–e**) respectively.

*7-(4-Chlorophenyl)-2-methylthio-5-phenyl-3H,4H-pyrido[2,3-d]pyrimidin-4-one (**10a**).* From compound **6a** (3.66 g, 10 mmol) and methyl iodide (1.72 g, 12 mmol). The compound was obtained as a white crystals, crystallized from dioxane in 87%; m.p. 273–275°C (dec.); ($C_{20}H_{14}ClN_3OS$) (379.8). IR (KBr) cm^{-1}: 3220 (NH), 1689 (C=O), 1657 (C=N); ^1H NMR (DMSO-d_6) ppm: δ 3.45 (s, 3H, SCH_3), 7.30–7.50 (m, 5H, phenyl proton), 7.65 (d, 2H), 7.75 (s, 1H, pyridine proton), 8.30 (d, 2H), 12.60 (br, s, NH, D_2O exchangeable). Mass; (70 ev) *m/z* (%): 379.1 (M^+, Cl^{35}, 100), 381.1 (M^+, Cl^{37}, 48.7), 332 (M^+–SMe, 9), 304 (M^+ + 2–C_6H_5, 65).

*2-(Acetylacetonethio)-7-(4-chlorophenyl)-5-phenyl-3H,4H-pyrido[2,3-d]pyrimidin-4-one (**10b**).* From compound **6a** (3.66 g, 10 mmol) and chloroacetylacetone (1.61 g, 12 mmol). The compound was obtained as a white powder, crystallized from dioxane in 81%; m.p. 206–208°C (melted); ($C_{24}H_{18}ClN_3O_3S$) (463.9). IR (KBr) cm^{-1}: 3301 (br, NH), 1743 (br, 2 C=O), 1682 (C=O), 1654 (C=N); Mass; (70 ev) *m/z* (%): 463 (M^+, 7), 421 (M^+ + 1-CH_3CO, 100), 378 (M^+-2 $COCH_3$, 78%), 332 (M^+-$SCH(COCH_3)_2$, 15%).

*2-[S-(N-4-Chlorophenylacetamido)]-7-(4-chlorophenyl)-5-phenyl-3H, 4H-pyrido[2,3-d]pyrimidin-4-one (**10c**).* From compound **6a** (3.66 g, 10 mmol) and 4-chloroacetanilide-2-chloride (2.04 g, 10 mmol). The compound was obtained as a white powder, crystallized from dioxane in 68%; m.p. 267–269°C (dec.); ($C_{27}H_{18}Cl_2N_4O_2S$) (497.8). IR (KBr) cm^{-1}: 1693, 1689 (2 C=O), 1658 (C=N); ^1H NMR (DMSO-d_6) ppm: δ 3.32 (br, s, NH, D_2O exchangeable), 3.65 (s, 2H, CH_2), 7.35–7.50 (m, 5H, phenyl proton), 7.65 (two mixed doublet, 4H), 7.82 (s, 1H, pyridine proton), 8.25 (two mixed doublet, 4H), 10.46 (br, s, NH, D_2O exchangeable).

*2-Acetylthio-7-(4-chlorophenyl)-3H,4H-pyrido[2,3-d]pyrimidin-4-one (**10d**).* From compound **6a** (3.66 g, 10 mmol) and chloroacetone (0.93 g, 10 mmol). The compound was obtained as a colorless crystals, crystallized from dioxane in 54%; m.p. 214–216°C (melted.); ($C_{22}H_{16}ClN_3O_2S$) (421.9). IR (KBr) cm^{-1}: 1720,, 1687 (2 C=O), 1659 (C=N); ^1H NMR (DMSO-d_6) ppm: δ 2.32, (s, 3H, CH_3), 3.61 (s, 2H, CH_2), 7.33–7.52 (m, 5H, phenyl proton), 7.67 (d, 2H), 7.78 (s, 1H, pyridine proton), 12.70 (br, s, NH, D_2O exchangeable).

*7-(4-Chlorophenyl)-2-phenacylthio-5-phenyl-3H,4H-pyrido[2,3-d]pyrimidin-4-one (**10e**).* From compound **6a** (3.66 g, 10 mmol) and phenacylbromide (1.99 g, 10 mmol). The compound was obtained as a white powder, crystallized from dioxane in 46% yield; m.p. 116–118°C

(melted.); ($C_{27}H_{18}ClN_3O_2S$) (483.9). IR (KBr) cm^{-1}: 1719, 1688 (2 C=O), 1657 (C=N); ^1H NMR (DMSO-d_6) ppm: δ 3.65 (s, 2H, CH_2), 7.40–7.55 (m, 10H, two phenyl proton), 7.63 (d, 2H), 7.72 (s, 1H, pyridine proton), 7.80 (s, NH, D_2O exchangeable), 8.28 (d, 2H).

*7-(4-Chlorophenyl)-2-hydrazino-3H,4H-pyrido[2,3-d]pyrimidin-4-one (**11**).* A suspension of compound **10a** (3.80 g, 10 mmol) in hydrazine hydrate (99%; 10 ml) was stirred under gentle reflux. The insoluble solid went into solution within 10 min with copious evolution of methylmercaptan to form a clear solution. After 30 min, when the solid product started separating out, heating continued for 4 h and the reaction mixture was allowed to cool to room temperature. The solid that separated was filtered, washed with ethanol, dried, and crystallized from dioxane/DMF (1:1) to produce a white powder in 83% yield; m.p. 313–315°C (melted.); ($C_{19}H_{14}ClN_5O$) (363.8). IR (KBr) cm^{-1}: 3290 (br, NH), 1689 (C=O), 1658 (C=N); ^1H NMR (DMSO-d_6) ppm: δ 3.31 (br, NH, D_2O exchangeable), 7.36–7.54 (m, 5H, phenyl proton), 7.61 (d, 2H), 7.89 (s, 1H, pyridine proton), 8.28 (d, 2H), 10.28 (br, s, NH, D_2O exchangeable).

*7-(4-Chlorophenyl)-2-(4-substituted phenylamino)-3H,4H-pyrido[2,3-d]pyrimidin-4-one (**12a**,**b**).*

General Procedure

A mixture of compound **10a** (3.80 g, 10 mmol) and substituted aniline (10 mmol) was heated at 140°C in a test tube on sand bath for 6 h. The mixture was allowed to cool to room temperature. The product was solidified by cooling and addition methanol (50 ml). The precipitate was collected by filtration and crystallized from the proper solvent to produce **12a**,**b**.

*7-(4-Chlorophenyl)-2-(4-chlorophenylamino)-3H,4H-pyrido[2,3-d]pyrimidin-4-one (**12a**).* From **10a** (3.80 g, 10 mmol) and 4-chloroaniline (1.28 g, 10 mmol). The compound was obtained as a white powder, crystallized from dioxane in 63% yield, m.p. 352–354°C (dec.); ($C_{25}H_{16}Cl_2N_4O$) (459.3). IR (KBr) cm^{-1}: 3235 (NH), 1679 (C=O), 1659 (C=N); ^1H NMR (DMSO-d_6) ppm: 7.38–7.56 (m, 5H, phenyl proton), 7.63 (d, 2H), 7.69 (d, 2H), 7.96 (s, 1H, pyridine proton), 8.18 (d, 2H), 8.26 (d, 2H), 9.58, 10.63 (two, br, s, NH, D_2O exchangeable). Mass; (70 ev) m/z (%): 458 (M^+—H, 7), 379.1 [(M^+-2)-C_6H_5, Cl^{35}, 100], 381 [(M^+-2)-C_6H, Cl,^{37}, 40], 350 [(M^+-2)-(C_6H_5 + CO), 21].

*7-(4-Chlorophenyl)-2-(4-nitrophenylamino)-3H,4H-pyrido[2,3-d]pyrimidin-4-one (**12b**).* From **10a** (3.80 g, 10 mmol) and 4-nitroaniline (1.38 g, 10 mmol). The compound was obtained as a white powder,

crystallized from dioxane in 67% yield, m.p. 325–327°C (dec.); ($C_{25}H_{16}ClN_5O_3$) (469.8). IR (KBr) cm^{-1}: 3243 (NH), 1683 (C=O), 1657 (C=N); ^1H NMR (DMSO-d_6) ppm: 7.43–7.58 (m, 5H, phenyl proton), 7.62 (d, 2H), 7.68 (d, 2H), 7.98 (s, 1H, pyridine proton), 8.21 (d, 2H), 8.29 (d, 2H), 9.36, 10.89 (two, br, s, NH, D_2O exchangeable). Mass; (70 ev) *m/z* (%): 469 (M^+, 35), 393 (M^+-C_6H_5, 42), 359 (M^+-C_6H_5Cl, 100).

2-Acetyl-8-(4-chlorophenyl)-3-methyl-6-phenyl-5H-thiazolo[3,2-a]pyrido[2,3-d]pyrimidin-5-one (13)

A solution of compound **10b** (4.64, 10 mmol) in a mixture of acetic anhydride-pyridine (20:10) ml was stirred under reflux for 3 h. The reaction mixture was allowed to cool to room temperature, then poured into cold water (100 ml). The deposited precipitate was filtered off, dried, and crystallized from dioxane. The compound was obtained as a light pale green crystals in 69% yield; m.p. 173–175°C (melted); ($C_{24}H_{16}ClN_5O_2S$) (445.9). IR (KBr) cm^{-1}: 1729, 1689 (2 C=O), 1663 (C=N); ^1H NMR (DMSO-d_6) ppm: 2.60 (s, 3H), 2.85 (s, 3H), 7.35–7.50 (m, 5H, phenyl proton), 7.60 (d, 2H), 7.80 (s, 1H, pyridine proton), 8.30 (d, 2H). Mass; (70 ev) *m/z* (%): 445.1 (M^+, Cl^{35}, 100), 447.1 (M^+, Cl^{37}, 37.6), 402 (M^+—$COCH_3$, 14), 363 (M^+-C_5H_6O, 40).

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