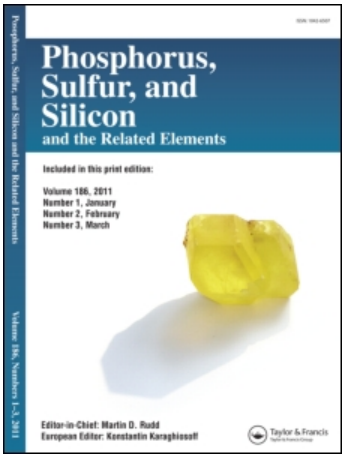

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Synthesis and Preliminary Antimicrobial Activity of New Pyrimido[4,5-*b*]-quinoline and Pyrido[2,3-*d*]pyrimidine

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Synthesis and Preliminary Antimicrobial Activity of New Pyrimido[4,5-*b*]-quinoline and Pyrido[2,3-*d*]pyrimidine

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*4-Chloro-2-methylthio-benzo[h]pyrimido[4,5-b]quinoline (**5**) and pyrido[2,3-d]-pyrimidine (**12**), were easily prepared from the cyclo-condensation of α,β-unsaturated ketones and 6-aminothiouracil. Compound **5** reacted with different amines to give 8-aryl-amino- (**6**,**7**), 2,4-dihydrazino-pyrimido[4,5-b]quinoline (**9**). Compound **7** was converted into benzo[h]-12,13-dihydrobenzo[a]-pyrimido[3′,2′:1,6]pyrimido[4,5-b]-quinoline (**8**) with a new ring system. The 2,4-dihydrazino- reacted with formic acid to afford benzo[h]-s-triazolo[4′,3′:1,6]-s-triazolo[3″,4″:2,3]pyrimido[4,5-b]quinoline (**10**) with a new ring system. Also, reaction of (**12**) with bromomalononitrile gave 3-amino-thiazolo[4,5-a]pyrido[2,3-d]pyrimidine-2-carbonitrile (**13**). Compound **13** reacted with formic acid, urea, thiourea, formamide to affording the pyrimido[4′,5′:-4,5]thiazolo[3,2-a]pyrido[2,3-d]pyrimidin-12-one (**14, 15, 16a,b, 21**) and reacted with carbon disulfide to give pyrido[2″,3″:4′,5′]pyrimido[2′,1′:2,3]thiazolo[4,5-d][1,3]-thiazine (**17**). Some of the synthesized derivatives exhibited, upon screening, antibacterial and antifungal activities.*

Keywords 4-Chlorobenzo[*h*]pyrimido[4,5-*b*]quinoline; benzo[*h*]-12,13-dihydro-benzo [*a*]pyrimido[3′,2′:1,6]pyrimido[4,5-*b*]quinoline; benzo[*h*]-*s*-triazolo-[4′,3′:1,6]-*s*-triazolo [3″,4″:2,3]pyrimido[4,5-*b*]quinoline

INTRODUCTION

Pyrimidine-containing molecules are of paramount importance in nucleic acid chemistry. Their derivatives, including uracil, cytosine, adenine, and guanine, are fundamental building blocks for deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Pyrimidine derivatives exist extensively in nature. They have biological and pharmaceutical activities. *N*-3-substituted pyrimidinones are potent AT1 selective angiotensin II receptor antagonists.[1]

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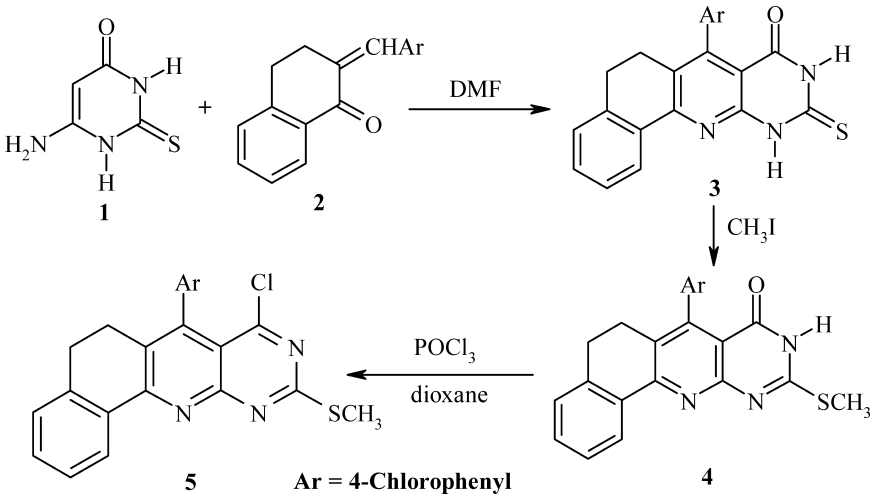


SCHEME 1

Pyrimidine amide derivatives are novel antiallergic agents.[2] S-alkylated derivatives are potent antiviral agents.[3] 6-Alkylamino-derivatives are inhibitors of bacillus subtilis DNA polymerase III.[4] Aziridino derivatives are new cytotoxic agents with tumor-inhibitory activity.[5] Arylamino derivatives of pyrimidines are potential anti-cytomegalovirus agents,[6] 2- or 4-(4-methylpiperazino)-pyrimidines are 5-HT2A receptor antagonists.[7] Due to the electronegativity of the two nitrogen atoms, pyrimidine is a 2-electron-deficient heterocycle. Therefore, nucleophilic displacements of nucleofugal leaving groups take place readily. This trend also translated to the 4-chloropyrimidoquinoline chemistry.

RESULTS AND DISCUSSION

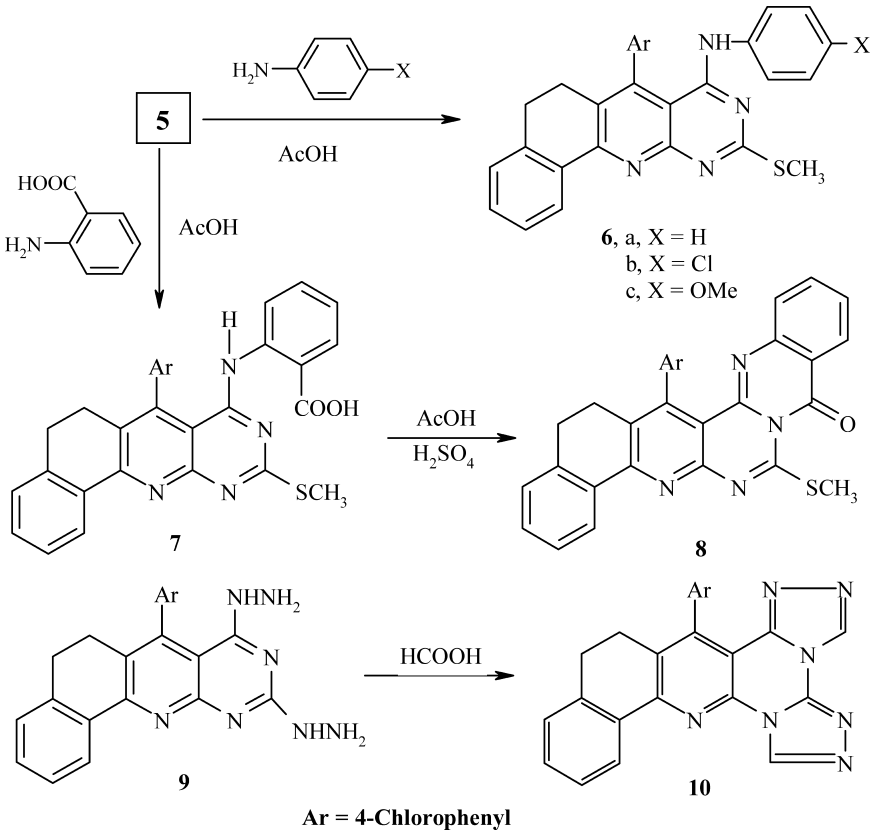
In this work, the synthesis of some poly-condensed heterocyclic based on pyrimido-quinoline and pyridopyrimidine are described. 6-Aminothiouracil **1** was reacted with α,β-unsaturated ketones **2** in dimethylformamide solution with stirring for a long time under thin layer chromatography control afforded 5-(4-aryl)-2-thioxo-1,3,6,7-tetrahydro-4*H*-benzo[*h*]pyrmido[4,5-*b*]quinolin-4-one derivatives (**3**) in good yield, Scheme 1.

It is well known in pyrimidines chemistry that position 4 in pyrimidines and fused pyrimidines shows distinct activities towards nucleophiles. Therefore, 4-chloro-2-methylthio-5-(4-chlorophenyl)-6,

7-dihydrobenzo[*h*]pyrimido[4,5-*b*]quinoline (**5**) was prepared by the method of *Shishoo*,[8] and its activity towards nucleophiles such as primary aromatic amines and hydrazine hydrates were investigated. Thus, heating under reflux compound **5** with arylamine, namely aniline, 4-chloroaniline and *p*-anisidine in acetic acid, produced the 4-arylamino-2-methylthio-5-(4-chlorophenyl)-6,7-dihydrobenzo [*h*]pyrimido[4,5-*b*]quinoline derivatives (**6a-c**). The IR and ^{1}H NMR ($CDCl_3$) spectrum of compound **5** revealed the absence of any absorption bands in the NH region. While the ^{1}H NMR (DMSO-d_6) spectrum of **6a** showed broad signal at 11.50 ppm corresponding the NH group, in addition to the sp3 and sp2 hydrogen atoms in the compound. Also the ^{1}H NMR (DMSO-d_6) spectrum of **6c** revealed the signal for OCH_3 at 3.87 ppm and the broad signal NH at 11.43 which exchangeable by D_2O in addition to the two duplet signals for the *p*-substituted phenyl at 7.00–7.08 and 7.63–7.75 ppm as AA′BB′ system with coupling constant $J = 13.2$ *Hz*.

Moreover, the reaction of 4-chloropyrimidoquinoline (**5**) with anthranilic acid in glacial acetic acid afforded 4-(*o*-carboxyphenyl)-aminopyrimidoqinoline derivative **7**. The IR spectra of **7** displayed an absorption band at 3520 cm^{-1} (OH), 3365 cm^{-1} (NH) and 1713 cm^{-1} for carbonyl group. Its ^{1}H NMR (DMSO-d_6) spectrum showed signals at δ 2.47–2.49 (t, 2H, CH_2), 2.73–2.78 (t, 2H, CH_2), 2.99 (s, 3H, SCH_3), 6.85–6.87 (d, 2H, phenyl), 7.07–7.10 (d, 2H, phenyl), 7.28–7.32 (m, 2H, phenyl), 7.37–7.41 (t, 2H, phenyl), 7.44–7.62 (m, 2H, phenyl), 7.64–7.99 (m, 2H, phenyl), 11.48 (brs, NH), and 12.13 (brs, OH). The latter compound **7** underwent cyclization when boiled with glacial acetic acid in presence of catalytic amount of sulfuric acid (1 ml) to give 7-(4-chlorophenyl)-benzo[*h*]-5,6-dihydrobenzo[*a*]pyrimido[3′,2′:1,6]pyrimido[4,-5-*b*]quinolin-13-one (**8**) with a new ring system, (Scheme 2). Structure **8** was preferred on the basis of ^{1}H NMR spectral data. Thus, ^{1}H NMR (DMSO-d_6) spectrum for the compound **8** showed signals at δ 2.45–2.48 (t, 2H, CH_2), 2.71 (s, 3H, SCH_3), 2.81–2.88 (t, 2H, CH_2), 7.21–7.22 (d, 2H, phenyl), 7.23–7.25 (m, 2H, phenyl), 7.27–7.29 (m, 2H, phenyl), 7.38–7.40 (t, 2H, phenyl), 7.44–7.69 (m, 2H, phenyl), and 8.30–8.31(d, 2H, phenyl).

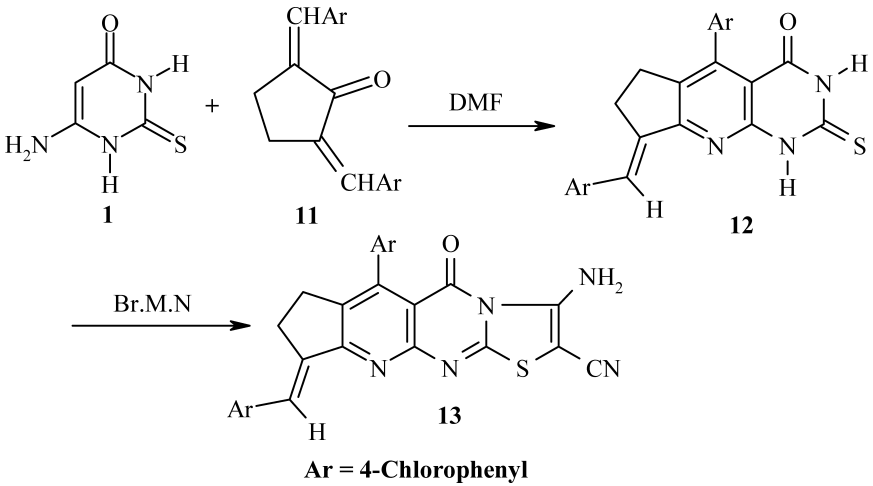
Similarly, the 2,4-dihydrazinopyrimidoquinoline derivative **9** was synthesized from **5** and hydrazine hydrate by heating in dry dioxane. The reactivity of **9** towards the aliphatic acids was studied. Where stirring it under reflux in formic acid afforded the 7-(4-chlorophenyl)-5,6-dihydrobenzo[*h*]-*s*-triazolo[4′,3′:1,6]-*s*-triazolo[3″,4″:2,3]-pyrimido[4,5-*b*]quinoline (**10**), with a new ring system. Beside the correct values of elemental analysis and spectral data of **9** are in agreement with the assigned structure. The IR spectrum of **9** displayed absorption bands



SCHEME 2

around 3438 cm^{-1} for NH's. While the IR spectrum of **10** revealed the absence of NH's groups. Also, the ^1H NMR (DMSO-d_6) spectrum of **9** showed the signals corresponding to NH_2's and NH's at δ 2.00, 10.70, and 11.60 ppm, which disappeared in compound **10,** in addition to the presence of two absorption bands at 9.23, 9.39 in compound **10** corresponding to the triazole proton was observed. Moreover, its ^{13}C NMR (DMSO-d_6) spectrum of **10** showed signals at δ 24.09, 26.98 two sp^3 carbon atoms and 19 sp^2 carbon atoms around 105.71–153.27 ppm, and its mass spectrum showed the molecular ion peak [M^+] at m/z 423 (100%).

Also, the pyridopyrimidine[9] as a part of our study designed to synthesize polyheterocyclic compounds possessing thiazolopyridopyrimidine derivatives containing enaminonitrile nucleus, which could be used as a precursor for the synthesis of a series of new compounds having new ring systems such as pyrimidothiazolopyridopyrimidine



SCHEME 3

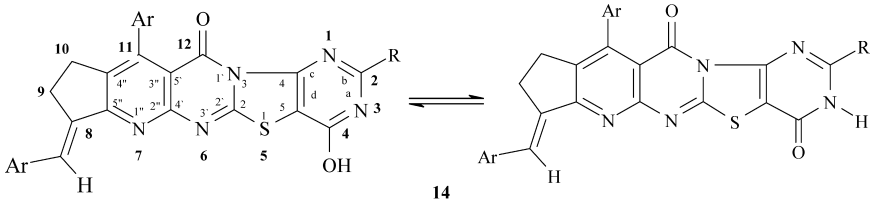
and pyridopyrimidothiazolothiazine. Thus, reaction of **12** with bromomalononitrile in aqueous alcoholic potassium carbonate solution, gave 3-amino-9-(4-arylmethylene)-6-(4-aryl)-1,2,10,11-tetrahydro-5*H*-thiazolo[4,5-*a*]cyclo-pentenopyrido[2,3-*d*]pyrimidine-2-carbonitrile-5-one (**13**) (Scheme 3).

Thiazolo[4,5-*a*]cyclopentenopyrido[2,3-*d*]pyrimidine-2-carbonitrile (**13**) was established on the following facts:

a) IR spectrum displayed absorption bands correspond to amino, cyano and carbonyl groups;
b) Compatible data in elemental analysis;
c) Compound **13** underwent characteristic reactions of β-enaminonitriles;
d) it was reported in the literature that N-3 and not N-1 nitrogen atom participates in cyclization of 2-substituted thiopyrimidine derivatives; [10]
e) the ^{1}H NMR (DMSO-d_6) spectrum of **13** showed signals at δ 2.63–2.74 (m, 2H, CH_2), 2.75–2.88 (m, 2H, CH_2), 7.16 (brs, NH_2), 7.46–7.48 (d, 2H, phenyl), 7.60–7.63 (d, 2H, phenyl), 7.63–7.65 (d, 2H, phenyl), 7.95–7.99 (d, 2H, phenyl), and 8.01 (s, 1H, methylenic proton);
f) its ^{13}C NMR (DMSO-d_6) spectrum showed signals δ 26.97, 28.06 for two sp^3 carbon atoms, one signals at 116.46 support to CN group, 18 signals corresponding to sp^2 carbon atoms around 108.48–158.68, and the signal of (C=O) at 163.88; and

g) its mass spectrum showed the absorption molecular ion peak [M^+], m/z 516, (100%), [M^{+2}–H_2N–C=C–CN], m/z 450 (17%).

Compound **13** as a typical β-enaminonitrile derivative, reacted with aliphatic acids namely, formic and acetic acids, afforded 8-(4-chlorophenylmethylene)-11-(chlorophenyl)-4-hydroxypyrimido[4′,5′:4,5]thiazolo[3,2-*a*]cyclopentenopyrido[2,3-*d*]pyrimidin-12-one derivatives (**14a,b**), with a new ring system.

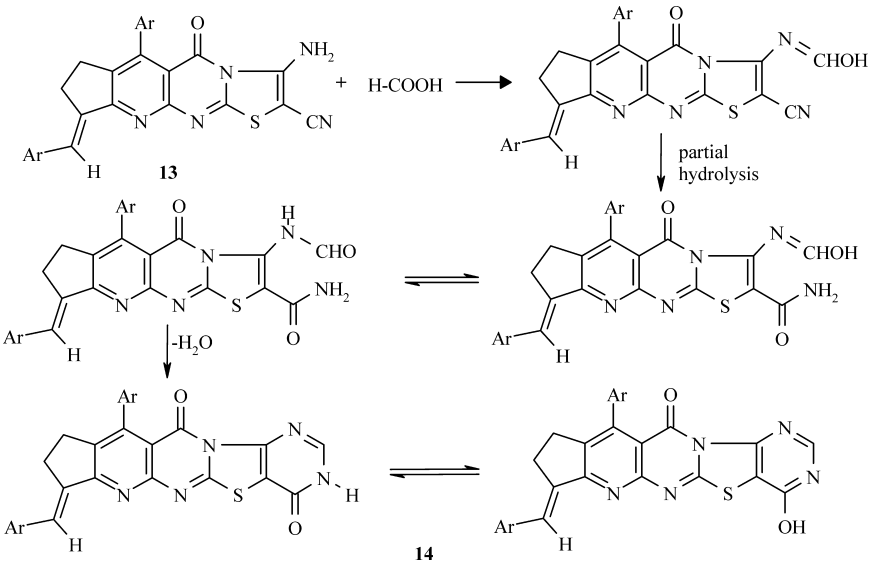


14
Ar = 4-Chlorophenyl
a, R = H ; b, R = Me

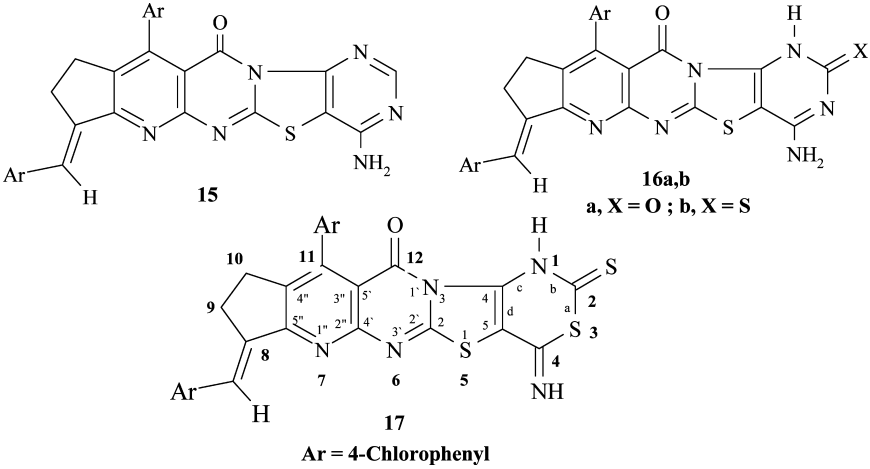
The IR spectrum of **14** displayed absorption bands around 3420 cm^{-1} (NH) and around 1696, 1689 for two carbonyl. Also, the ^1H NMR (DMSO-d_6) spectrum of compound **14b** as an example showed signals at δ 2.32 (s, 3H, CH_3), 2.75–2.78 (t, 2H, CH_2), 2.85–2.97 (t, 2H, CH_2), 7.10–7.12 (d, 2H, phenyl), 7.39–7.41 (d, 2H, phenyl), 7.42–7.44 (d, 2H,), 7.45–7.47 (d, 2H, phenyl), 8.02 (s, 1H, methylenic proton), 10.00 (brs, NH, D_2O exchangeable). Formation of **14** from **13** and formic acid may proceed as shown in Scheme 4.

Similarly, compound **13** reacted with formamide, in the presence of formic acid and dimethylformamide, to yield 4-amino-9,10-dihydropyrimido[4′,5′:4,5]-thiazolo[3,2-*a*]cyclopentenopyrido[2,3-*d*]pyrimidin-12-one derivative (**15**).

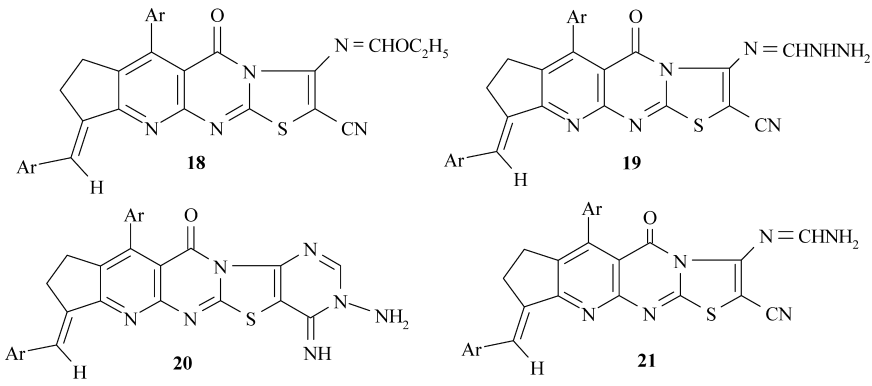
The ^1H NMR (DMSO-d_6) spectrum of **15** showed the signals at δ 2.68–2.73 (t, 2H, CH_2), 2.88–3.00 (t, 2H, CH_2), 7.21–7.26 (d, 2H, phenyl), 7.28–7.39 (d, 2H, phenyl), 7.41–7.44 (d, 2H, phenyl), 7.51–7.57 (d, 2H, phenyl), 7.95 (s, 1H, methylenic proton), 8.15 (s, 1H, pyrimidine), and 8.35 (brs, NH_2). Also, when heated compound **13** with urea or thiourea at 180°C, it gave 4-amino-pyrimido[4′,5′:4,5]thiazolo[3,2-a]-cyclopentenopyrido[2,3-*d*]pyrimidine-2,12-dione (**16a**), and the 4-amino-pyrimido-[4′,5′:4,5]thiazolo[3,2-*a*]cyclopentenopyrido[2,3-*d*] pyrimidine-2-thioxo-12-one **16b**, respectively (Scheme 5). The ^1H NMR (DMSO-d_6) spectrum of **16b** showed signals at δ 2.71–2.73 (t, 2H, CH_2), 3.02–3.05 (t, 2H, CH_2), 7.26–7.28 (d, 2H, phenyl), 7.30–7.39 (d, 2H, phenyl), 7.43–7.45 (d, 2H, phenyl), 7.50–7.53 (d, 2H, phenyl), 7.56 (s, 1H, methylenic), 11.87 (brs, NH), and 12.55 (brs, NH). Also, its IR



SCHEME 4



SCHEME 5



Ar = 4-Chlorophenyl

SCHEME 6

spectrum for the compounds **16a,b** displayed absorption bands around 3395 (NH) and 1686 cm^{-1} (CO).

On the other hand, when compound **13** was heated with carbon disulphide in pyridine, 1,2,9,10-tetrahydro-4*H*-10*H*-cyclopentenopyrido[2″,3″:4′,5′]pyrimido[2′,1′-:2,3]thiazolo[4,5-*d*][1,3] thiazine-12-one (**17**),[11] with a new ring system, was obtained. The ^1H NMR (DMSO-d_6) spectrum of **17** showed signals at δ 2.73–2.78 (t, 2H, CH_2), 3.20–3.32 (t, 2H, CH_2), 6.97–6.99 (d, 2H, phenyl), 7.09–7.12 (d, 2H, phenyl), 7.29–7.41 (d, 2H, phenyl), 7.42–7.44 (d, 2H, phenyl), 8.26 (s, 1H, methylenic), and 12.10, 12.95 (two broads band, 2NH, D_2O exchangeable). Moreover, its IR spectrum displayed absorption bands at 3400 cm^{-1} (NH), 1685 cm^{-1} (CO).

Condensation of **13** with triethyl orthoformate, yielded the corresponding 3-ethoxymethyleneamino-1,2,10,11-tetrahydro-5*H*-thiazolo [4,5-*a*]cyclopentenopyrido-[2,3-*d*]pyrimidine-2-carbonitrile-5-one derivative **18**, with compatible IR and ^1H NMR data. The latter compound reacted with hydrazine hydrate in boiling dioxane, to give 3-hydrazinomethyleneamino-1,2,10,11-tetrahydro-5*H*-thiazolo[4,5-*a*] cyclopent-enopyrido[2,3-*d*]pyrimidine-2-carbonitrile-5-one**19**, which on boiling in ethanolic sodium ethoxide solution, underwent cyclization to give 3-amino-4-imino-3,4,9,10-tetrahydropyrimido[4′,5′:4,5]thiazolo [3,2-*a*]cyclopentenopyrido[2,3-*d*]pyrimidin-12-one (**20**), (Scheme 6).

The IR spectrum of **18** displayed absorption bands at 2213 cm^{-1}(CN), while that of **20** revealed the absence of CN group. The ^1H NMR (DMSO-d_6) spectrum of **20**, showed signals at δ 2.68–2.73 (t, 2H, CH_2), 2.88–3.00 (t, 2H, CH_2), 7.19–7.27 (d, 2H, phenyl), 7.36–7.39 (d, 2H, phenyl) 7.40–7.43 (d, 2H, phenyl), 7.44–7.46 (d, 2H, phenyl), 8.26

(s, 1H, methylenic), 8.29 (s, 1H, pyrimidine proton), 10.82 (brs, NH_2, D_2O exchangeable), and 11.30 (brs, NH, D_2O exchangeable).

Finally, compound **18** was heated with ammonium hydroxide solution, in boiling ethanol, it gave 3-aminomethyleneamino-1,2,10,11-tetrahydro-5*H*-thiazolo-[4,5-*a*]cyclopentenopyrido[2,3-*d*]pyrimidine-2-carbonitrile-5-one (**21**). The IR spectrum of **21** displayed absorption bands at 3395, 3310 cm^{-1} (NH_2), 2216 cm^{-1} (CN) and 1694 cm^{-1}(CO), and that ^1H NMR (DMSO-d_6) spectrum of **21** showed signals at δ 2.66–2.70 (t, 2H, CH_2), 2.80–3.00 (t, 2H, CH_2), 6.97–7.00 (d, 2H, phenyl), 7.11–7.16 [m, 3H,(d, 2H, phenyl + 1H, methylenic)], 7.23–7.31 (d, 2H, phenyl), 7.45–7.50 (d, 2H, phenyl), 8.43 (s, 1H, methylenic proton), and 12.55 (brs, NH, D_2O exchangeable). Moreover, the latter compound **21** could be converted into **15** upon heating in ethanolic sodium ethoxide solution.

Antimicrobial Activity

Twenty compounds were screened in vitro for their antimicrobial activities against four strains of bacteria species namely *Staphylococcus aureus* (ATCC 29737),*Bacillus subtilis* (NCIMB8054), *Escherichia coli* (NCTC10418), and Salmonella typhi and two strains of fungi Aspergillus terrus and Aspergillus Flavus by the agar diffusion technique.[12] A 1mg/mL solution in dimethylformamide was used. The bacteria and fungi were maintained on nutrient agar and Czapek,s-Dox agar media, respectively. DMF showed no inhibition zones. The agar media were inoculated with different microorganisms culture tested. After 24 h incubation at 30°C for bacteria and 48 h of incubation at 28°C for fungi, the diameter of inhibition zone (mm) was measured (Table I). Chloramphenicol in a concentration (25 μgm^{-1}, and Grisofluvine (30 μgm^{-1}); used as a references for antibacterial and antifungal activities respectively. The minimal inhibitory concentration (**MIC**) of some of the tested compounds was measured by a two fold serial dilution method.[13] The most of the synthesized compounds exhibited various antimicrobial activity towards all the micro-organisms used.

CONCLUSIONS

The prepared new ring systems seem to be interesting for biological activity studies. Furthermore, the present investigation offers rapid and effective new routes for the synthesis of poly-condensed heterocyclic based on pyrimidoquinolines and pyridopyrimidine derivatives.

TABLE I Antimicrobial Activity of Some Synthesized Compounds and Inhibition Zones

		Gram (−) bacteria		Gram (+) bacteria		Fungi	
Compd. no	C.*	E.Coli	Salmonella typhi	Staphylococcus aureus	Bacillus subtillus	Aspergillus terrus	Aspergillus flavus
6a	1	+	+	++	+	++	++
	2.5	+	+	+	+	+	+
	5	+	+	+	+	+	+
8	1	++	+	+	+	++	++
	2.5	++	+	+	+	+	++
	5	+	+	+	+	+	+
10	1	+	+	+	+	+	+
	2.5	++	+	+	+	+	+
	5	++	+	+	++	+	+
13	1	+	+	+	+	+	+
	2.5	+	+	+	+	+	+
	5	++	+	+	+	+	+
14b	1	++	+	++	++	++	++
	2.5	+	+	+	++	+	++
	5	+	+	+	+	+	+
15	1	+	+	+	+	++	++
	2.5	+	+	+	+	++	++
	5	+	+	+	+	++	++
16a	1	++	+	++	+	++	++
	2.5	+	+	++	+	+	++
	5	+	+	+	+	+	+
17	1	+	++	+	+	+	+
	2.5	+	++	+	+	+	+
	5	+	+	+	+	+	+
20	1	++	++	++	++	++	++
	2.5	++	++	++	++	++	++
	5	++	++	++	++	++	++
St.	1	++	+++	+++	++	++	+++
	2.5	+++	+++	+++	+++	+++	+++
	5	+++	+++	+++	+++	+++	+++

*C = Concentration of the sample in mg/ml; + = Inhibition values = 0.1–0.5 cm beyond control; ++ = Inhibition values = 0.6–1.0 cm beyond control; and +++ = Inhibition values = 1.1–1.5 cm beyond control.

EXPERIMENTAL

All melting points are uncorrected and measured using an Electrothermal IA 9100 apparatus (Shimadzu, Japan). The ^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL JNM-LA-400 FT NMR Spectrometer (Universitat Konstanz, Germany) and chemical shifts were expressed as δ values against $SiMe_4$ as internal standards. IR spectra

were recorded as KBr pellets on a Perkin-Elmer 1430 spectrometer, (National Research Center and Department of Chemistry Cairo University). Mass spectra were recorded on GCMS-Q P1000 EX Shimadzu Japan (Gas Chromatography-Mass spectrometer). Microanalytical data were performed by the Microanalytical Center at Cairo University (Egypt). The starting materials are prepared according to *Quiroga*[14] and *El-Gazzar*.[15,16] The biological evaluation of the products was carried out at the Fermentation Biotechnology & Applied Microbiology (Ferm- BAM) Center at Al-Azhar University, Cairo, Egypt.

4-Chloro-2-methylthio-5-(4-chlorophenyl)-6,7-dihydrobenzo[h]pyrimido[4,5-b]-quinoline (5)

A solution of compound **4** (4.05 g, 10 mmol) in dry dioxane (30 mL) was treated with 7 ml of phosphorus-oxychloride and the mixture was stirred under reflux for 3 h, the reaction mixture was allowed to cool to room temperature. It was poured into cold water (100 mL), whereby a solid was separated, filtered off, and crystallized from dioxane (yellow powder), in 56% yield, m.p. 313+ + −315°C (melted); **IR**, cm^{-1}: 3029 (CH aryl), 2919 (CH alkyl), 1601 (C=N), 1520 (C=C), 1160 (C-Cl); ^1H NMR ($CDCl_3$) ppm: δ 2.29 (s,3H, S-CH_3) 2.46–2.50 (m, 2H, CH_2), 2.74–2.78 (m, 2H, CH_2), 7.06–7.09 (d, 2H, phenyl), 7.13–7.17 (d, 2H, phenyl), 7.29–7.35 (m, 1H, phenyl), 7.41–7.46 (m, 2H, phenyl), 8.30–8.33 (m, 1H, phenyl); **Analysis**: $C_{22}H_{15}Cl_2N_3S$ (424.3); **Requires**: **C**, 62.26;**H**, 3.56; **N**, 9.90. **Found**: **C**, 62.19; **H**, 3.61; **N**, 9.84.

4-Arylamino-2-methylthio-5-(4-chlorophenyl)-6,7-dihydrobenzo[h]pyrimido[4,5-b]-quinoline (6a-c)—General Procedure

In a warm solution of compound **5** (4.24 g, 10 mmol) in glacial acetic acid (40 ml), the freshly distilled arylamine (10 mmol) was added. The reaction mixture was stirred under reflux for 3 h, allowed to cool to 0°C for 4 h, and the solid obtained was filtered, washed with water (100 mL) dried, and crystallized from appropriate solvent to produce (**6a,b**) in high yields.

5-(4-Chlorophenyl)-4-phenylamino-2-methylthio-6,7-dihydrobenzo[h]pyrimido-[4,5-b]quinoline (6a)

The compound was obtained from **5** (4.24 g, 10 mmol) and aniline (0.93 g, 10 mmol), as pale yellow crystals, crystallized from dixane/dimethylformamide (1:1) in 67% yield, m.p. 385–389°C (melted); **IR**,

cm^{-1}: 3400 (brs NH), 3042 (CH aryl), 2931 (CH alkyl), 1601 (C=N), 1520 (C=C).^{1}**H NMR** (DMSO-d_6) ppm: δ δ 2.31 (s,3H, S-CH_3) 2.47–2.51(m, 2H, CH_2), 2.75–2.78 (m, 2H, CH_2), 7.05–7.08 (d, 2H, phenyl), 7.11–7.15 (d, 2H, phenyl), 7.20–7.39 [m, 6H, (1H, phenyl + 5H, phenyl)], 7.40–7.46 (m, 2H, phenyl), 8.30–8.33 (m, 1H, phenyl), 11.50 (brs, NH, D_2O exchangeable). **Analysis**: $C_{28}H_{21}ClN_4S$ (480.9); **Requires**: **C**, 69.91; **H**, 4.40; **N**, 11.65. **Found**: **C**, 69.79; **H**, 4.33; **N**, 11.56.

4-(Chlorophenylamino)-5-(4-chlorophenyl)-2-methylthio-6,7-dihydrobenzo[h]-pyrimido[4,5-b]quinoline (6b)

The compound was obtained from **5** (4.24 g, 10 mmol) and 4-chloroaniline (1.27 g, 10 mmol), as yellow crystals, crystallized from dimethylformamide in 71% yield, m.p. 292–294°C (melted); **IR**, cm^{-1}: 3395 (brs, NH), 3039 (CH aryl), 2926 (CH alkyl), 1617 (C=N), 1532 (C=C).^{1}**H NMR** (DMSO-d_6) ppm: δ 2.28 (s,3H, S-CH_3) 2.45–2.51 (m, 2H, CH_2), 2.75–2.79 (m, 2H, CH_2), 7.08–7.10 (d, 2H, phenyl), 7.16–7.23 (2d, 4H, phenyl), 7.30–7.34 (m, 1H, phenyl), 7.42–7.46 (m, 2H, phenyl), 7.65–7.78 (d, 2H, phenyl), 8.29–8.32 (m, 1H, phenyl), 11.43 (brs, NH, D_2O exchangeable). **Analysis**: $C_{28}H_{20}Cl_2N_4S$ (515.4); **Requires**: **C**, 65.24; **H**, 3.91; **N**, 10.87. **Found**: **C**, 65.19; **H**, 3.90; **N**, 10.76.

5-(4-Chlorophenyl)-4-(4-methoxyphenylamino)-2-methylthio-6,7-dihydrobenzo[h]-pyrimido[4,5-b]quinoline (6c)

The compound was obtained from **5** (4.24 g, 10 mmol) and 4-anisidine (1.23 g,10 m mol), as yellow crystals, crystallized from dimethylformamide in 76% yield, m.p. 270–272°C (melted); **IR**, cm^{-1}: 3390 (brs, NH), 3021 (CH aryl), 2916 (CH alkyl), 1614 (C=N), 1523 (C=C). ^{1}**H NMR** (DMSO-d_6) ppm: δ 2.29 (s,3H, S-CH_3) 2.46–2.52 (m, 2H, CH_2), 2.74–2.78 (m, 2H, CH_2), 3.87 (s, 3H, OCH_3) 7.00–7.08 (d, 2H, pheny, J = 13.0 *Hz*), 7.12–7.18 (two duplet, 4H, phenyl), 7.23–7.29 (m, 1H, phenyl), 7.42–7.47 (m, 2H, phenyl), 7.63–7.75 (d, 2H, phenyl, J = 13.2 *Hz*), 8.26–8.29 (m, 1H, phenyl), 11.43 (brs, NH, D_2O exchangeable). **Analysis**: $C_{29}H_{23}ClN_4OS$ (511.0); **Requires**: **C**, 68.15; **H**, 4.53; **N**, 10.96. **Found**: **C**, 68.09; **H**, 4.51; **N**, 10.87.

4-(o-Carboxyphenyl)amino-5-(4-chlorophenyl)-2-methylthio-6,7-dihydrobenzo[h]-pyrimido[4,5-b]quinoline (7)

In a warm solution of compound **5** (4.24 g, 10 mmol) in glacial acetic acid (30 ml) was added (1.37 g, 10 mmol) of anthranilic acid. The reaction mixture was stirred under reflux for 5 h, then allowed to cool to

0°C for 5 h, and the solid obtained was filtered off, washed with water (100 ml) dried, and crystallized from dioxane in 74% yield, m.p. 311–313°C (melted); **IR**, cm^{-1}: 3520 (brs, OH), 3365 (NH), 3051 (CH aryl), 2917 (CH alkyl), 1713 (CO), 1604 (C=N); ^{1}**H NMR** (DMSO-d_6) ppm: δ 2.47–2.49 (t, 2H, CH_2), 2.73–2.78 (t, 2H, CH_2), 2.99 (s, 3H, SCH_3), 6.85–6.87 (d, 2H, phenyl), 7.07–7.10 (d, 2H, phenyl), 7.28–7.32 (m, 2H, phenyl), 7.37–7.41 (t, 2H, phenyl), 7.44–7.62 (m, 2H, phenyl), 7.64–7.99 (m, 2H, phenyl), 11.48 (brs, NH), and 12.13 (brs, OH). **Analysis**: $C_{29}H_{21}ClN_4O_2S$ (525.0); **Requires**: **C**, 66.34; **H**, 4.03; **N**, 10.67. **Found**: **C**, 66.23; **H**, 4.00; **N**, 10.54.

7-(4-Chlorophenyl)-benzo[h]-5,6-dihydrobenzo [a]pyrimido[3′,2′:1,6]pyrimido[4,5-b]quinolin-13-one (8)

A solution of compound **7** (5.26 g, 10 mmol) in glacial acetic acid (40 mL) and catalytic amount of sulfuric acid (1 mL) was stirred under reflux for 8 h. The reaction mixture was allowed to cool, poured into cold water (100 mL), neutralized by ammonia solution, the precipitate was filtered off washed with water, dried and crystallized from dimethylformamide (yellow crystals) in 65% yield, m.p. 356–358°C (dec.); **IR**, cm^{-1}: 3039 (CH aryl), 2908 (CH alkyl), 1701 (CO), 1631 (C=N); ^{1}**H NMR** (DMSO-d_6) ppm: δ 2.45–2.48 (t, 2H, CH_2), 2.71 (s, 3H, SCH_3), 2.81–2.88 (t, 2H, CH_2), 7.21–7.22 (d, 2H, phenyl), 7.23–7.25 (m, 2H, phenyl), 7.27–7.29 (m, 2H, phenyl), 7.38–7.40 (t, 2H, phenyl), 7.44–7.69 (m, 2H, phenyl), and 8.30–8.31(d, 2H, phenyl). **Analysis**: $C_{29}H_{19}ClN_4OS$ (506.9); **Requires**: **C**, 68.70; **H**, 3.78; **N**, 11.05. **Found**: **C**, 68.67; **H**, 3.75; **N**, 10.96.

5-(4-Chlorophenyl)-2,4-dihydrazino-6,7-dihydrobenzo[h]pyrimido[4,5-b]quinoline (9)

A mixture of compound **5** (4.24 g, 10 mmol) and hydrazine hydrate (99–100%) (10 ml) was stirred under reflux in dioxane (30 mL) and ethanol (5 ml) for 5 h. The reaction mixture was allowed to cool to 0°C for 5 h, the solid was collected by filtration and crystallized from dioxane (pale yellow powder) in 79% yield, m.p. 207–210°C (melted); **IR**, cm^{-1}: 3438 (brs, NH), 3039 (CH aryl), 2928 (CH alkyl), 1624 (C=N); ^{1}**H NMR** (DMSO-d_6) ppm: δ 2.00 (brs, 2H, NH_2, D_2O exchangeable), 2.45–2.50 (m, 2H, CH_2), 2.75–2.78 (m, 2H, CH_2), 7.05–7.09 (d, 2H, phenyl), 7.14–7.18 (d, 2H, phenyl), 7.27–7.34 (m, 1H, phenyl), 7.40–7.45 (m, 2H, phenyl), 8.32–8.35 (m, 1H, phenyl), 10.70, 11.60 (two, brs, 2NH, D_2O exchangeable). **Analysis**: $C_{21}H_{18}ClN_7$ (403.8); **Requires**: **C**, 62.45;**H**, 4.49; **N**, 24.28. **Found**: **C**, 62.38; **H**, 4.51; **N**, 24.19.

7-(4-Chlorophenyl)-5,6-dihydrobezo[h]-s-triazolo[4′,3′:1,6]-s-triazolo[3″,4″:2,3]-pyrimido[4,5-b]quinoline (10)

A mixture of compound **9** (4.03 g, 10 mmol), formic acid (20 ml) and catalytic amount of concentrated hydrochloric acid was heated under reflux for 20 h. The reaction mixture was allowed to cool to room temperature and poured into cold water (100 ml). The solid formed was collected by filtration, washed with water, ethanol, dried, and crystallized from dimethylformamide (white powder) in 68% yield, m.p. 340–342°C (dec.); **IR**, cm^{-1}: 3026 (CH aryl), 2935 (CH alkyl), 1631 (C=N), 1560 (C=C); ^{1}**H NMR** (DMSO-d_6) ppm: δ 2.46–2.50 (m, 2H, CH_2), 2.74–2.78 (m, 2H, CH_2), 7.02–7.08 (d, 2H, phenyl), 7.13–7.17 (d, 2H, phenyl), 7.28–7.34 (m, 1H, phenyl), 7.40–7.45 (m, 2H, phenyl), 8.31–8.34 (m, 1H, phenyl), 9.23 (s, 1H, triazole proton), 9.39 (s, 1H, triazole proton).^{13}**C NMR** (DMSO-d_6) ppm: δ 24.09, 26.98 (2C, $2CH_2$) 105.71, 125.76, 126.00, 126.34, 127.36, 127.80, 128.21, 128.42, 129.53, 130.67, 130.78, 132.96, 136.55, 139.18, 148.23, 148.56, 149.78, 150.09, 153.27 (19C, sp^2 carbon atoms). Its **MS**, [M^+] m/z 423 (100%). **Analysis**: $C_{23}H_{14}ClN_7$ (423.8); **Requires**: **C**, 65.17; **H**, 3.33; **N**, 23.13. **Found**: **C**, 65.13; **H**, 3.26; **N**, 23.08.

3-Amino-9-(4-chlorophenylmethylene)-6-(4-chlorophenyl)-1,2,10,11-tetrahydro-5H-thiazolo[4,5-a]cyclopentenopyrido[2,3-d]pyrimidine-2-carbonitrile-5-one (13)

A mixture of compound **12** (4.52 g, 10 mmol), bromomalononitrile (1.45 g, 10 mmol) and potassium carbonate anhydrous (2.76 g, 20 mmol) was stirred under reflux in 30 mL ethanol for 12 h (under TLC control). The reaction mixture was allowed to cool to room temperature and then poured into cold water (100 mL). The precipitate was filtered off, dried, and crystallized from benzene, brown crystals, in 56% yield, m.p. 330–332°C (dec.); **IR**, cm^{-1}: 3451 (brs, NH_2), 3091 (CH aryl), 2921 (CH, alkyl), 2214 (CN), 1690 (CO), 1643 (C=N), 1521 (C=C); ^{1}**H NMR** (DMSO-d_6) ppm: δ 2.63–2,74 (m, 2H, CH_2), 2.75–2.88 (m, 2H, CH_2), 7.16 (brs, NH_2),7.46–7.48 (d, 2H, phenyl), 7.60–7.63 (d, 2H, phenyl), 7.63–7.65 (d, 2H, phenyl), 7.95–7.99 (d, 2H, phenyl), and 8.01 (s, 1H, methylenic proton). ^{13}**C NMR** (DMSO-d_6) ppm: δ. 26.97, 28.06 (2C, $2CH_2$), 66.46 (1C, CN), 108.48, 125.04, 127.79, 128.07, 128.71, 128.77, 129.27, 129.51, 130.79, 131.00, 132.60, 135.25, 135.64, 135.89, 141.58, 147.92, 152.77, 158.68 (19C, sp^2 carbon atoms) and 163.88 (CO); Its **MS**, [M^+], m/z 516, (100%), [M^{+2}-H_2N-C=C-CN], m/z 450 (17%); **Analysis**: $C_{26}H_{15}Cl_2N_5OS$ (516.4); **Requires**: **C**, 60.47; **H**, 2.92; **N**, 13.56. **Found**: **C**, 60.43; **H**, 2.90; **N**, 13.60.

8-(4-Chlorophenylmethylene)-11-(chlorophenyl)-4H-9,10-dihydropyrimido[4′,5′:-4,5]thiazolo[3,2-a] cyclopentenopyrido[2,3-d]pyrimidine-4,12-dione (14a)

A mixture of compound **13** (5.16 g, 10 mmol), formic acid (10 mL) and catalytic amount of concentrated hydrochloric acid was heated under reflux for 16 h. The reaction mixture was allowed to cool to room temperature, poured into cold water (100 mL). The formed solid was collected by filtration, washed by ethanol (20 mL), dried, and crystallized from ethanol (pale brown) in 66% yield, m.p. 359–362°C (melted); **IR**, cm^{-1}: 3406 (brs, NH), 3096 (CH aryl), 2941 (CH alkyl), 1693, 1687 (2CO), 1643 (C=N), 1529 (C=C); ^{1}**H NMR** (DMSO-d_6) ppm: δ 2.68–2.86 (m, 2H, CH_2), 3.02–3.14 (m, 2H, CH_2), 7.25–7.31 (d, 2H, phenyl), 7.42–7.45 (2d, 4H, phenyl), 7.51–7.55 (d, 2H, phenyl), 7.62 (s, 1H, methylenic proton), and 13.20 (brs, NH, D_2O exchangeable); **Analysis**: $C_{27}H_{15}Cl_2N_5O_2S$ (544.4); **Requires**: **C**, 59.56; **H**, 2.77; **N**, 12.86. **Found**: **C**, 59.60; **H**, 2.68; **N**, 12.90.

8-(4-Chlorophenylmethylene)-11-(chlorophenyl)-4H-2-methyl-9,10-dihydropyri-mido[4′,5′:4,5]thiazolo[3,2-a]cyclopentenopyrido[2,3-d]pyrimidine-4,12-dione (14b)

A mixture of compound **13** (5.16 g, 10 mmol), acetic acid (30 mL) was heated under reflux for 20 h. The reaction mixture was allowed to cool to room temperature, poured into cold water (100 mL). The formed solid was collected by filtration, washed by ethanol (20 mL), dried, and crystallized from ethanol (brown powder) in 67% yield, m.p. 275–277°C (melted); **IR**, cm^{-1}: 3420 (brs, NH), 3084 (CH aryl), 2939 (CH alkyl), 1696, 1689 (2CO), 1639 (C=N), 1521 (C=C); ^{1}**H NMR** (DMSO-d_6) ppm: δ 2.32 (s, 3H, CH_3), 2.75–2.78 (t, 2H, CH_2), 2.85–2.97 (t, 2H, CH_2), 7.10–7.12 (d, 2H, phenyl), 7.39–7.41 (d, 2H, phenyl), 7.42–7.44 (d, 2H, phenyl), 7.45–7.47 (d, 2H, phenyl), 8.02 (s, 1H, methylenic proton), 10.00 (brs, NH). **Analysis**: $C_{28}H_{17}Cl_2N_5O_2S$ (558.4); **Requires**: **C**, 60.21; **H**, 3.07; **N**, 12.54. **Found**: **C**, 62.39; **H**, 2.99; **N**, 12.60.

4-Amino-8-(4-chlorophenylmethylene)-12-(chlorophenyl)-9,10-dihydropyrimido-[4′,5′:4,5]thiazolo[3,2-a]cyclopentenopyrido[2,3-d]pyrimidin-12-one (15)

Method (A)

A mixture of compound (**13**) (5.16 g, 10 mmol), formamide (0.45 g, 10 mmol) and formic acid (2 mL) was stirred under reflux in dimethylformamide (20 mL) for 6 h. The reaction mixture was allowed to cool

to room temperature, poured into water (100 mL) neutralized by ammonia solution. The precipitate was collected by filtration washed by water, ethanol, dried, and crystallized from dioxane in 64% yield, m.p. 295°C (dec.); **IR**, cm^{-1}: 3390 (brs, NH), 3076 (CH aryl), 2952 (CH alkyl), 1693 (CO), 1663 (NH_2), 1656 (C=N), 1545 (C=C); **^{1}H NMR** (DMSO-d_6) ppm: δ 2.68–2.73 (t, 2H, CH_2), 2.88–3.00 (t, 2H, CH_2), 7.21–7.26 (d, 2H, phenyl), 7.28–7.39 (d, 2H, phenyl), 7.41–7.44 (d, 2H, phenyl), 7.51–7.57 (d, 2H, phenyl), 7.95 (s, 1H, methylenic proton), 8.15 (s, 1H, pyrimidine proton), and 11.30 (brs, NH). **Analysis**: $C_{27}H_{16}Cl_2N_6OS$ (543.4); **Requires**: **C**, 59.67; **H**, 2.96; **N**, 15.46. **Found**: **C**, 59.70; **H**, 2.89; **N**, 15.38.

Method (B)

To a warmed ethanolic sodium ethoxide solution (prepared by dissolving (0.23 g, 10 mmol) sodium metal in 50 mL absolute ethanol) was added (5.43, 10 mmol) of compound (**21**). The mixture was stirred under reflux for 5 h. The reaction mixture was allowed to cool to room temperature, poured into cold water (100 mL), neutralized by acetic acid. The precipitate was filtered off, dried and crystallized from dioxane in 45% yield, m.p. 293–296°C (dec.), with the same identical data.

4-Amino-8-(4-chlorophenylmethylene)-12-(chlorophenyl)-9,10-dihydropyrimido-[4′,5′:4,5]thiazolo[3,2-a]pyrido[2,3-d] pyrimidine-2-(oxo/or thioxo)-12-ones (16a,b)— General Procedure

A mixture of compound **13** (5.16 g, 10 mmol) and urea or thiourea (10 mmol) was heated at 180°C in test tube on sand-bath for 4 hours. The mixture was allowed to cool to room temperature; the product was solidified by cooling and addition of methanol (50 mL). The precipitate formed was collected by filtration and crystallized from the proper solvent to produce (**16a,b**).

4-Amino-8-(4-chlorophenylmethylene)-12-(chlorophenyl)-9,10-dihydropyrimido-[4′,5′:4,5]thiazolo[3,2-a]cyclopentenopyrido [2,3-d]pyrimidine-2,12-dione (16a)

The compound was obtained from **13** and urea (0.61g, 10 mmol), as a dark brown, crystallized from dimethylformamide in 71% yield, m.p. 345–346°C (melted.); **IR**, cm^{-1}: 3410 (brs, NH), 3079 (CH aryl), 2938 (CH alkyl), 1694, 1686 (2CO), 1654 (C=N), 1530 (C=C); **^{1}H NMR** (DMSO-d_6) ppm: δ 2.72–2.88 (m, 2H, CH_2), 3.04–3.15 (m, 2H, CH_2), 7.29–7.32 (d, 2H, phenyl), 7.45–7.48 (2d, 4H, phenyl),

7.54–7.57 (d, 2H, phenyl), 7.82 (s, 1H, methylenic proton) 12.30 (brs, NH, D_2O exchangeable), and 13.01 (brs, NH, D_2O exchangeable). **Analysis**: $C_{27}H_{16}Cl_2N_6O_2S$ (559.42); **Requires**: **C**, 57.96; **H**, 2.88; **N**, 15.02. **Found**: **C**, 58.01; **H**, 2.89; **N**, 15.11.

4-Amino-8-(4-chlorophenylmethylene)-12-(chlorophenyl)-9,10-dihydropyrimido-[4′,5′:4,5]thiazolo[3,2-a]cyclopentenopyrido [2,3-d]pyrimidine-2-thioxo-12-one (16b)

The compound was obtained from **13** and thiourea (0.77 g, 10 mmol), as a brown crystals, crystallized from dioxane in 62% yield, m.p. 330°C (dec.); **IR**, cm^{-1}: 3397 (brs, NH), 3084 (CH aryl), 2929 (CH alkyl), 1683 (CO), 1658 (C=N), 1526 (C=C); ^{1}**H NMR** (DMSO-d_6) ppm: δ 2.71–2.73 (t, 2H, CH_2), 3.02–3.05 (t, 2H, CH_2), 7.26–7.28 (d, 2H, phenyl), 7.30–7.39 (d, 2H, phenyl), 7.43–7.45 (d, 2H, phenyl), 7.50–7.53 (d, 2H, phenyl), 7.56 (s, 1H, methylenic proton), 11.87 (brs, NH), and 12.55 (brs, NH). **Analysis**: $C_{27}H_{16}Cl_2N_6OS_2$ (575.5); **Requires**: **C**, 56.34; **H**, 2.80; **N**, 14.60. **Found**: **C**, 56.36; **H**, 2.78; **N**, 14.39.

8-(4-Chlorophenylmethylene)-11-(4-chlorophenyl)-1,2,9,10-tetrahydro-4H-10H-cyclopentenopyrido[2″,3″:4′,5′] pyrimido [2′,1′:2,3]thiazolo[4,5-d][1,3]thiazine-12-one (17)

A mixture of compound 13 (5.16 g,10 mmol) and carbon disulphide (excess 10 mL) was heated under reflux on a water-bath (80°C) in 20 mL pyridine for 8 h (under TLC control). The reaction mixture was allowed to cool to 0°C for 3 h, the precipitate was filtered off, washed by ethanol (20 mL), dried, and crystallized from dioxane in 59% yield, m.p. 283°C (dec.); IR, cm^{-1}: 3400 (brs, NH), 3096 (CH aryl), 2947 (CH alkyl), 1685 (CO), 1661 (C=N), 1535 (C=C); ^{1}H NMR (DMSO-d_6) ppm: δ 2.73–2.78 (t, 2H, CH_2), 3.20–3.32 (t, 2H, CH_2), 6.97–6.99 (d, 2H, phenyl), 7.09–7.12 (d, 2H, phenyl), 7.29–7.41 (d, 2H, phenyl), 7.42–7.44 (d, 2H, phenyl), 8.26 (s, 1H, methylenic proton), and 12.10, 12.95 (2brs, 2NH, D_2O exchangeable). Analysis: $C_{27}H_{15}Cl_2N_5OS_3$ (592.5); Requires: C, 54.72; H, 2.55; N, 11.82. Found: C, 54.80; H, 2.57; N, 11.79.

3-Ethoxymethyleneamino-9-(4-chlorophenylmethylene)-6-(4-chlorophenyl)-1,2,10,-11-tetrahydro-5H-thiazolo[4,5-a] cyclopentenopyrido[2,3-d]pyrimidine-2-carbo-nitrile-5-one (18)

A mixture of compound **13** (5.16 g, 10 mmol) and triethylorthoformate (2.96 g, 20 mmol) was stirred under reflux in acetic anhydride (30 mL)

for 6 h. The reaction mixture was allowed to cool to room temperature, poured into cold water (100 mL) and neutralized by ammonia solution. The precipitate was collected by filtration, washed by water, dried and crystallized from methanol in 70% yield, m.p. 236–238°C (melted); **IR**, cm^{-1}: 3390 (brs, NH), 3086 (CH aryl), 2924 (CH alkyl), 2213 (CN), 1690 (CO), 1650 (C=N), 1523 (C=C).^{1}**H NMR** (DMSO-d_6) ppm: δ 1.24–1.28 (t, 3H, CH_3), 2.56–2.58 (t, 2H, CH_2) 2.81–2.84 (t, 2H, CH_2), 4.38–4.43 (q, 2H, CH_2), 7.24–7.28 (d, 2H, phenyl), 7.38–7.40 (d, 2H, phenyl), 7.44–7.48 (d, 2H, phenyl), 7.5–7.63 (d, 2H, phenyl), 8.20 (s, 1H, methylenic proton), 8.44 (s, 1H, CH). **Analysis**: $C_{29}H_{19}Cl_2N_5O_2S$ (572.4); **Requires**: **C**, 60.84; **H**, 3.34; **N**, 12.23. **Found**: **C**, 60.91; **H**, 3.38; **N**, 12.18.

3-Hydrazinomethyleneamino-9-(4-chlorophenylmethylene)-6-(4-chlorophenyl)-1,2,-10,11-tetrahydro-5H-thiazolo[4,5-a] cyclopentenopyrido[2,3-d]pyrimidine-2-carbo-nitrile-5-one (19)

A mixture of compound **18** (5.72 g, 10 mmol), hydrazine hydrate (99–100%) (10 mL) was stirred under reflux in a mixture of dioxane/ethanol (20 mL/5 mL) for 8 h. The reaction mixture was allowed to cool to room temperature, poured into cold water (100 mL), neutralized by acetic acid. The precipitate was collected by filtration, washed by water, dried and crystallized from dioxane in 68% yield, m.p. 289–291°C (melted); **IR**, cm^{-1}: 3420 (brs, NH), 3069 (CH aryl), 2934 (CH alkyl), 2218 (CN), 1683 (CO), 1640 (C=N), 1553 (C=C).^{1}**H NMR** (DMSO-d_6) ppm: δ 2.72–2.87 (m, 2H, CH_2), 3.03–3.16 (m, 2H, CH_2), 7.28–7.31 (d, 2H, phenyl), 7.38–7.45 (2d, 4H, phenyl), 7.48–7.53 [t, 3H, (d, 2H, phenyl + s, 1H, methylenic)], 7.56 (s, 1H, methylenic proton) 12.30 (brs, NH, D_2O exchangeable), and 13.00 (brs, NH, D_2O exchangeable). **Analysis**: $C_{27}H_{17}Cl_2N_7OS$ (558.4); **Requires**: **C**, 58.06; **H**, 3.07; **N**, 17.55. **Found**: **C**, 58.03; **H**, 3.11; **N**, 17.48.

3-Amino-8-(4-chlorophenylmethylene)-12-(chlorophenyl)-4-imino-3,4,9,10-tetra-hydropyrimido[4′,5′:4,5]thiazolo[3,2-a]cyclopentenopyrido[2,3-d]pyrimidin-12-one (20)

To a warmed ethanolic sodium ethoxide solution (prepared by dissolving (0.23 g, 10 mmol) sodium metal in 50 mL absolute ethanol) was added (5.58 g, 10 mmol) of compound **19**. The mixture was stirred under reflux for 8 h. The reaction mixture was allowed to cool to room temperature, poured into cold water (100 mL), neutralized by acetic acid. The deposited so-precipitate was filtered off, dried, and crystallized from

benzene in 67% yield, m.p. 316–318°C (melted); **IR**, cm^{-1}: 3400 (brs, NH), 3091 (CH, aryl), 2937 (CH, alkyl), 1692 (CO), 1635 (C=N), 1546 (C=C); ^{1}**H NMR** (DMSO-d_6) ppm: δ 2.68–2.73 (t, 2H, CH_2), 2.88–3.00 (t, 2H, CH_2), 7.19–7.27 (d, 2H, phenyl), 7.36–7.39 (d, 2H, phenyl), 7.40–7.43 (d, 2H, phenyl), 7.44–7.46 (d, 2H, phenyl), 8.26 (s, 1H, methylenic proton), 8.29 (s, 1H, pyrimidine proton), 10.82 (brs, 2H, NH_2) and 11.30 (brs, NH). **Analysis**: $C_{27}H_{17}Cl_2N_7OS$ (558.4); **Requires**: **C**, 58.07; **H**, 3.06; **N**, 17.55. **Found**: **C**, 58.10; **H**, 3.09; **N**, 17.63.

3-Aminomethyleneamino-9-(4-chlorophenylmethylene)-6-(4-chlorophenyl)-1,2,10,-11-tetrahydro-5H-thiazolo[4,5-a] cyclopentenopyrido[2,3-d]pyrimidine-2-carbo-nitrile-5-one (21)

A mixture of compound **18** (5.72 g, 10 mmol) and ammonia solution (40–50%) (10 mL) was stirred under reflux in 50 mL ethanol for 12 h. The reaction mixture was allowed to cool to room temperature, poured into cold water (100 mL), and neutralized by acetic acid. The deposited so-precipitate was filtered off, washed with water, dried and crystallized from dimethylformamide in 52% yield, m.p. 337–339°C (dec.); **IR**, cm^{-1}: 3395, 3310 (brs, NH_2), 3091 (CH aryl), 2932 (CH alkyl), 2216 (CN), 1694 (CO), 1647 (C=N), 1550 (C=C).^{1}**H NMR** (DMSO-d_6) ppm: δ 2.66–2.70 (t, 2H, CH_2), 2.80–3.00 (t, 2H, CH_2), 6.97–7.00 (d, 2H, phenyl), 7.11–7.16 [m, 3H, (2H, phenyl + 1H, methylenic)], 7.23–7.31 (d, 2H, phenyl), 7.45–7.50 (d, 2H, phenyl), 8.43 (s, 1H, methylenic proton) and 12.55 (brs, NH, D_2O exchangeable). **Analysis**: $C_{27}H_{16}Cl_2N_6OS$ (543.4); **Requires**: **C**, 59.67; **H**, 2.96; **N**, 15.46. **Found**: **C**, 59.71; **H**, 3.00; **N**, 15.50.

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