Scientific paper

A Simple Synthesis and Antimicrobial Activity of Sulfur-containing Poly-condensed Heterocyclic Derivatives from 1,3-benzothiazole

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Abstract

A novel series of 7-amino-5-aryl-6-(benzothiazol-2-yl)-2-thioxopyrido[2,3-*d*]pyrimidin-4-one derivatives was prepared and their reactivity towards some reagents was studied. Transformations of aromatic aldehydes, halogens and some hydrazonoyl chlorides towards the corresponding poly-condensed heterocyclic compounds, such as 8-amino-7-(benzothiazol-2-yl)-[1,3]thiazolo[4,5-*a*]pyrido[2,3-*d*]pyrimidine-3,5-diones, 3,9-diarylisoazolo[5´,4´:4,5]thiazolo-[3,2-*a*]pyrido[2,3-*d*]pyrimidin-10-ones and 1,6-diaryl and 3-aryl- or 3-acetyl- or 3-ethylcarboxylate- derivatives of 7-(benzothiazol-2-yl)-pyrido[2,3-*d*][1,2,4]triazolo[4,5-*a*]pyrimidin-5-ones were investigated. Compounds synthesized were screened *in vitro* for their antimicrobial activity against a variety of bacterial and fungal agents.

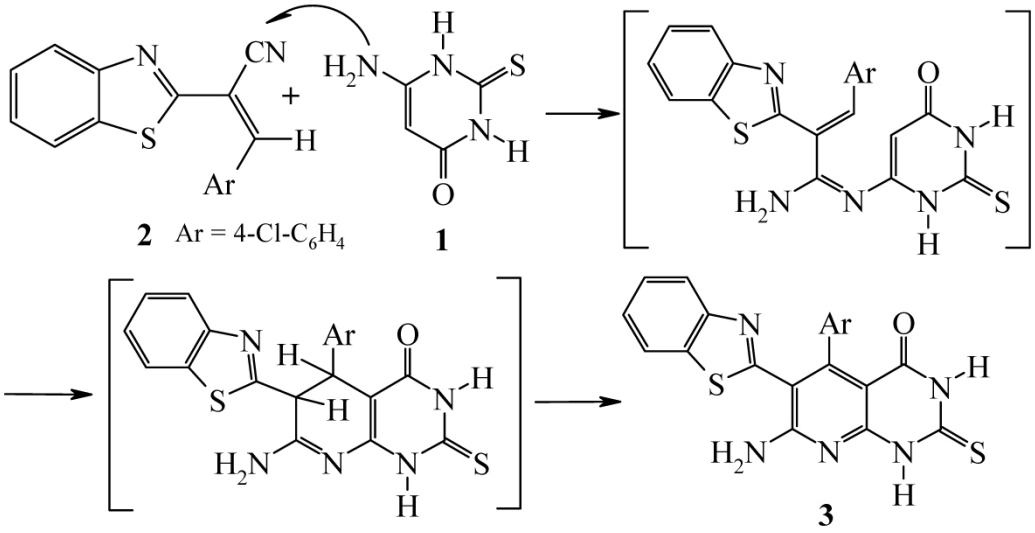
Keywords: 7-Amino-, 8-amino-, 6-(benzothiazole)isooxazolo[5´,4´:4,5]thiazolopyridopyrimidine, antimicrobial activities.

1. Introduction

Bacterial infections often induce pain and inflammation. In normal practice, two groups of agents (chemotherapeutic, analgesic and anti-inflammatory) are prescribed simultaneously. Unfortunately, none of drugs available possesses these activities in a single component. Recent literature is enriched with progressive findings about the synthesis and pharmacological action of fused heterocycles. Heterocycles bearing a pyrimidine and pyrido[2,3-*d*]pyrimidine moieties are reported to show a broad spectrum of pharmacological properties, such as antimicrobial,[1–4] and central nervous system (CNS) activities, analgesic and anti-inflammatory activities.[5–8] Recent reports have shown that pyrido[2,3-*d*]-pyrimidines (bioisosteres of pyrimidine) posses CNS and antibacterial activities.[9,10] Exploiting the bioisosterism concept, we have shown that 3-amino-6-phenyl-7,8,9,10-tetrahydro[1,2,-4]triazolo[4',3':1,2]pyrimido[4,5-*b*]quinolin-5-one and pyrido[2,3-*d*]pyrimidine derivatives[11] exhibit anti-oxidant, analgesic and anti-inflammatory activities. The present work is an extension of our ongoing efforts[12–14] towards the development and identification of new molecules via the concept of bioisosterism; we have aimed to synthesize some novel 7-amino-6-(benzothiazol-2-yl)-pyrido[2,3-*d*]pyrimidine and 8-amino-7-(benzothiazol-2-yl)-[1,3]thiazolo[4,5-*a*]pyrido[2,3-*d*]pyrimidine-3,5-dione derivatives as well as isooxazolothiazolopyridopyrimidines and screened them for antimicrobial activities.

2. Results and Discussion

Condensation of 6-aminothiouracil (**1**) with 2-benzylidenecyanomethyl-1,3-benzothiazole **2** in dimethylformamide afforded the corresponding 7-amino-5-aryl-6-(benzothiazol-2-yl)-pyrido[2,3-*d*]-pyrimidine **3**. (Scheme 1) The latter pyrido[2,3-*d*]pyrimidine was used as a key compound for this study and for further syntheses of other fused heterocycles. The IR spectrum of compound **3** showed the presence of the amino group and MS gave the characteristic fragmentation pattern due to the presence of the chlorine atom in compound **3**. The ^{13}C NMR showed 16 signals between 100.3–159.5 ppm for 18 sp^2 carbon atoms (16 nonequivalent carbons), a signal at 163.4 for carbonyl group and a signal at 175.7 belonging to the thioxo group (C=S).



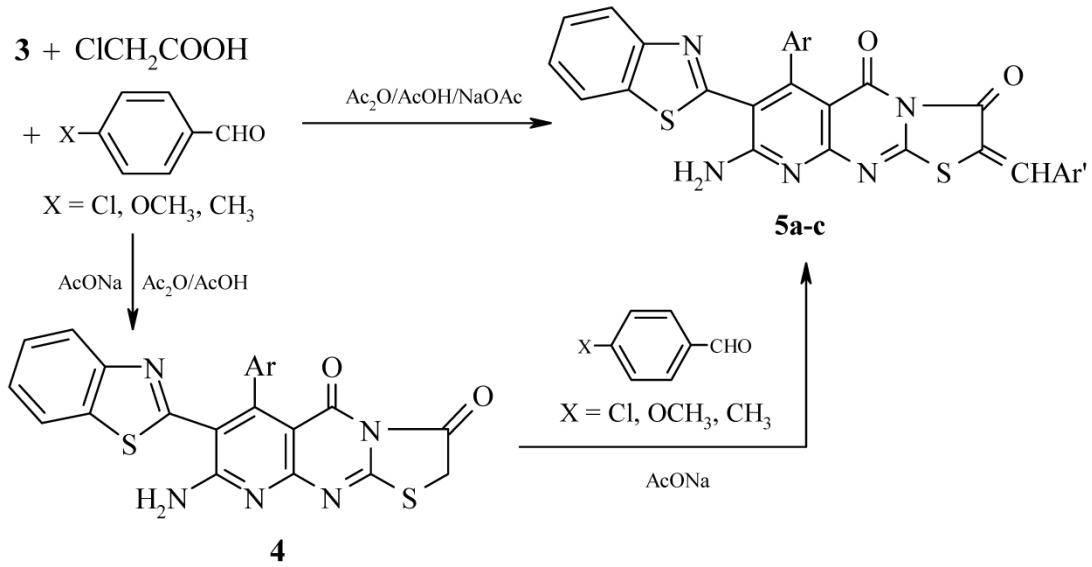
Scheme 1

Ar = 4-Cl-C_6H_4

Compound **3** was condensed with aromatic aldehydes in a ternary mixture of chloroacetic acid, acetic acid and acetic anhydride, in the presence of anhydrous sodium acetate to give 2-arylmethylene-8-amino-6-(4-chlorophenyl)-7-(benzothiazol-2-yl)-[1,3]thiazolo[4,5-*a*]pyrido[2,3-*d*]pyrimidine-3,5-dione derivatives **5a**–**c** in high yield as shown in Scheme 2.

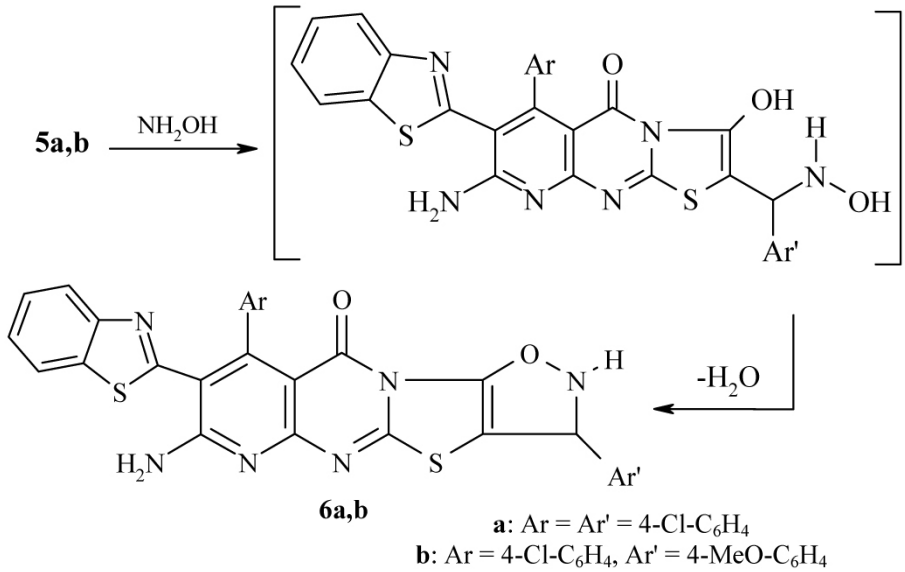
However, gently heating the latter mixture in the absence of aldehyde gave 8-amino-6-(4-chlorophenyl)-7-(benzothiazol-2-yl)-[1,3]thiazolo[4,5-*a*]pyrido[2,3-*d*]pyrimidine-3,5-dione (**4**), which was further condensed with aldehydes in acetic acid and anhydrous sodium acetate to give 2-arylmethylene derivatives **5**.

lucidation of structures **4** and **5** is based on the correct values of elemental analyses and appropriate spectral data (^{1}H and ^{13}C NMR). As an example, the ^{1}H NMR spectrum of **5a** showed the following signals: 7.23 (d, 2H), 7.26 (d, 1H), 7.29–7.31 (2×d, 3H), 7.36 (t, 1H), 7.68 (d, 2H), 8.03 (d, 1H), 8.28 (d, 2H), 8.51 (s, 1H) and 8.76 (brs, 2H). The ^{13}C NMR of **5b** showed a signal at δ 55.4 corresponding to the CH_3 group, 23 nonequivalent sp^2 carbons with signals between 100.3–159.3 ppm and two signals at 162.7 and 163.9 supporting the two carbonyl groups. IR spectrum of **4** displayed absorption bands at 1688 and 1676 cm^{-1} for two carbonyl groups. Moreover, compounds **5a**,**b** underwent cycloaddition with hydroxylamine hydrochlo-



a: Ar = Ar' = 4-Cl-C_6H_4
b: Ar = 4-Cl-C_6H_4, Ar' = 4-MeO-C_6H_4
c: Ar = 4-Cl-C_6H_4, Ar' = 4-Me-C_6H_4

Scheme 2



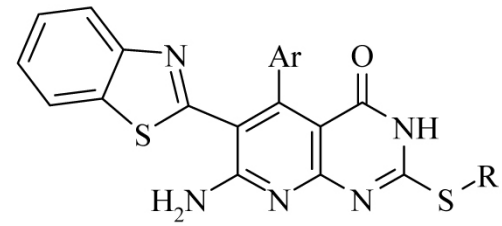
Scheme 3

ride (by heating in boiling acetic acid in the presence of anhydrous sodium acetate) to give 3,9-diaryl-isooxazolo[5´,4´:4,5]thiazolo[3,2-*a*]pyrido[2,3-*d*]-pyrimidin-10-ones **6a**,**b**.

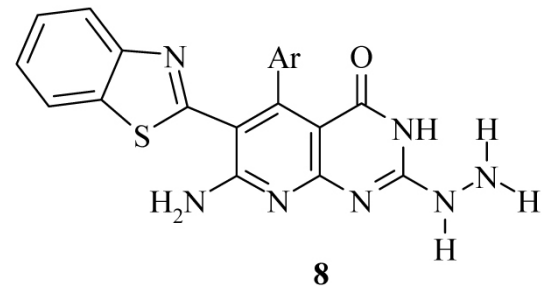
The ^{1}H NMR spectrum of **6b**, as an example, showed the following signals: 3.96 (s, 3H), 6.02 (d, 1H), 7.23 (d, 2H), 7.27 (d, 1H), 7.30–7.33 (2×d, 3H), 7.36–7.39 (m, 1H), 7.60 (d, 2H), 8.02 (d, 1H), 8.30 (d, 2H), 8.68 (brs, 2H) and 9.80 (br, 1H). The ^{13}C NMR of **6b** showed a signal at 55.5 ppm for methyl group, a signal at 70.7 ppm corresponds to the C-3 in isooxazole ring, signals between 101.3–159.3 correspond to 23 sp^2 carbon atoms and a signal at 163.9 from the carbonyl group. Moreover, the IR spectrum of **6a**,**b** displayed absorption bands at 3250 (NH) and 1685 cm^{-1} (CO). The formation of isooxazolo[5´,4´:4,5]thiazolo[3,2-*a*]-pyrido[2,3-*d*]pyrimidin-10-one **6** from 8-amino-thiazolo[4,5-*a*]pyrido[2,3-*d*]pyrimidine-3,5-dione **5** may proceeded first by 1,4-addition of hydroxylamine on the ethylenic double bond followed by the loss of water as shown in Scheme 3.

Alkylation of an ethanolic potassium hydroxide solution of **3** with halogen compounds yielded 2-alkylthio derivatives **7a**–**d**, respectively. Assignment of structures **7** is based on the fact that each of **7a**,**b** gave upon treatment with hydrazine hydrate the same 2-hydrazino derivative **8** (with concomitant evolution of methyl or ethyl mercaptan). The ^{1}H NMR spectrum for the compound **7b**, as an example, showed signals at 1.37 and 2.86 corresponding to the ethyl group.

The reaction of **3** in an ethanolic potassium hydroxide solution with -haloketones, such as chloroacetone and phenacyl bromide, yielded 7-amino-2-(*S*-acetone or *S*-phenacyl)-6-(benzothiazol-2-yl)-pyrido[2,3-*d*]pyrimidin-4*(4H)*-ones **9a**,**b**. Assignment of structures **9a**,**b** is based on correct elemental analyses. IR spectra are in agreement with the structures and reveal the presence of two carbonyl groups (peaks around 1685 and 1715 cm^{-1}). The ^{1}H-NMR spectrum for compound **9a** showed two singlet signals at 1.75 and 4.28 corresponding to the CH_3 and CH_2 groups, respectively.



7a-d



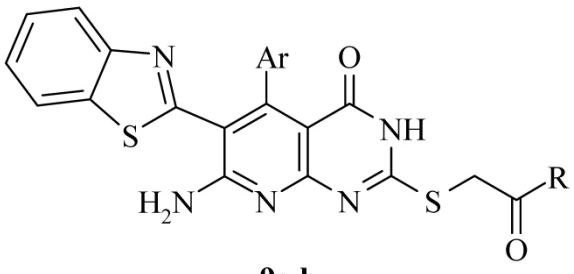
8

Ar = 4-Cl-C$_6$H$_4$

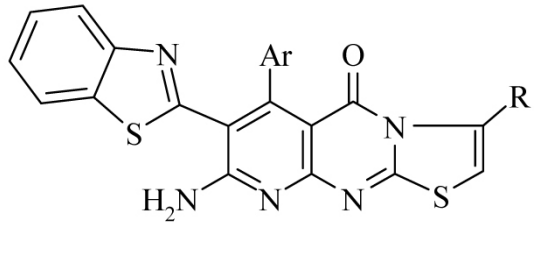
a: R = CH_3; **b**: R = C_2H_5; **c**: R = $CH_2CONH(4\text{-Cl-}C_6H_4)$;

d: R = $CH(COCH_3)_2$

Compounds **9a**,**b** underwent cyclization when boiled with glacial acetic acid in the presence of a catalytic amount of sulphuric acid to give 8-amino-3-(methyl or phenyl)-7-(benzothiazol-2-yl)-thiazolo[4,5-*a*]pyrido[2,3-*d*]pyrimidin-5-ones **10a**,**b**. Structures **10a**,**b** were elucidated on the basis of ^{1}H NMR and ^{13}C NMR spectral data.



9a,b



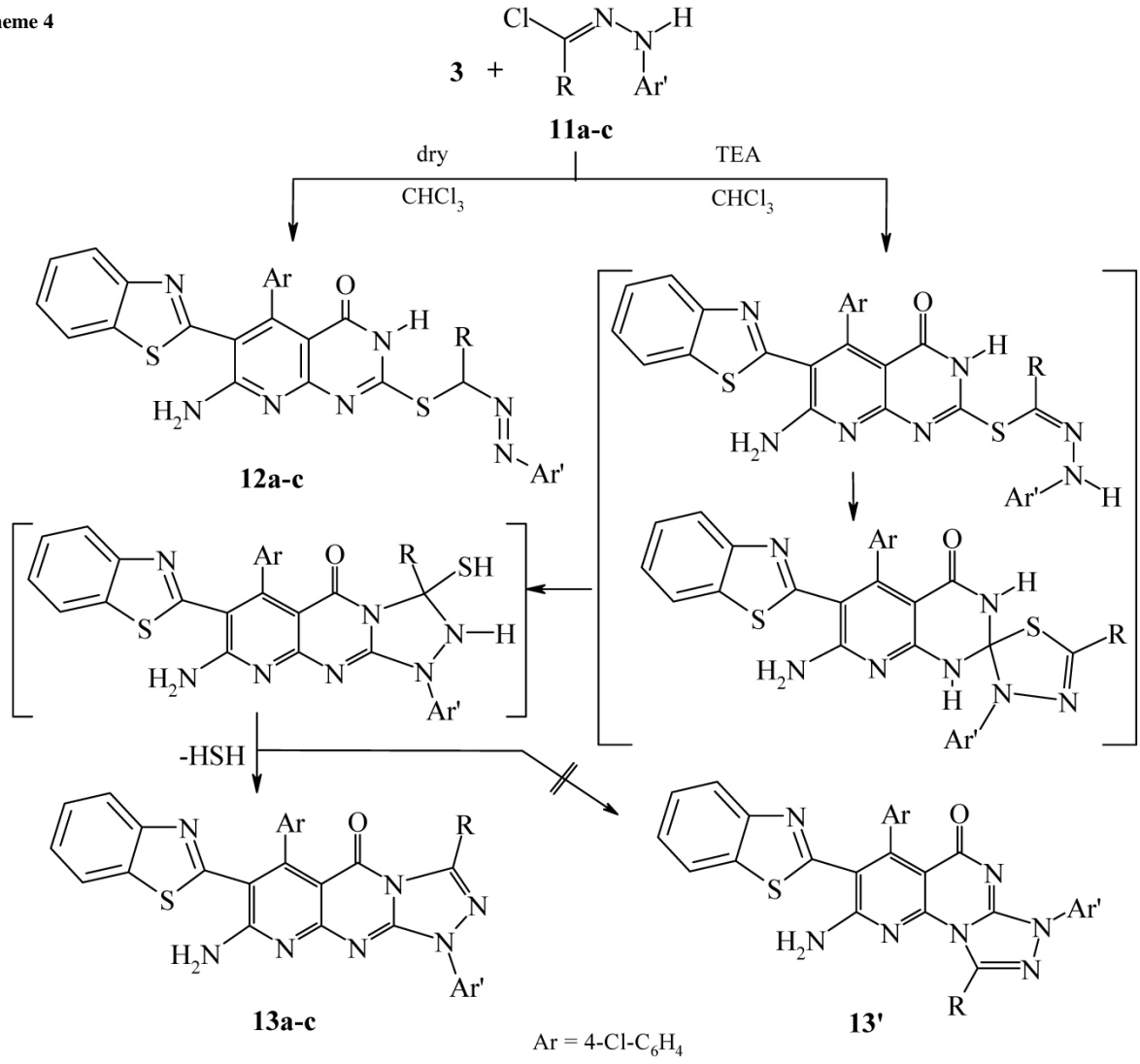
10a,b

Ar = 4-Cl-C_6H_4

a: R = CH_3; **b**: R = C_6H_5

Thus, ^{1}H NMR spectrum of the compound **10b** showed signals at 6.97 (d, 2H), 7.13 (d, 1H), 7.40–7.78 (m, 5H), 8.00–8.12 (m, 3H), 8.33 (d, 2H), 8.41 (s, 1H) and 8.92 (brs, 2H). Moreover, stirring compound **3** under reflux with hydrazonoyl chlorides **11a–c** in dry chloroform afforded 2-[*S*-(acetonyl-1-phenylazo)]-6-(benzothiazol-2-yl)-pyrido[2,3-*d*]pyrimidin-4-ones **12a**,**b** and 2-*S*-ethyl-[1-tollylazo)-6-(benzothiazol-2-yl)-pyrido[2,3-*d*]pyrimi-

Scheme 4

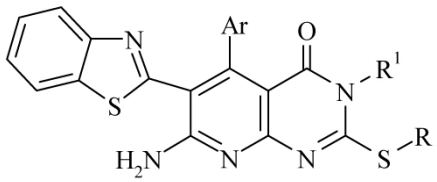


a: Ar' = R = C_6H_5; **b**: Ar' = 4-Cl-C_6H_4, R = $COCH_3$; **c**: Ar' = 4-Me-C_6H_4, R = $COOC_2H_5$

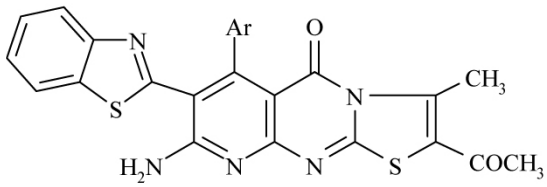
din-4(4*H*)-4-one]carboxylate **12c**. Whereas the stirring of the same reactants under reflux in dry chloroform in the presence of triethylamine as a base and catalyst for a long time afforded the cyclized product (after removal of hydrogen sulfide) 6-(4-chlorophenyl)-(1-aryl and 3-aryl or 3-acetyl or 3-ethylcarboxylate)-7-(benzothiazol-2-yl)-pyrido[2,3-*d*][1,2,4]triazolo[4,5-*a*]pyrimidin-5-ones **13a–c** and not **13'**, as shown in Scheme 4.

IR and ^{1}H NMR spectra of **12a–c** gave data in agreement with the proposed structures. The ^{1}H NMR spectrum of **12c**, as an example, showed signals between 1.27–4.42 which supported the two methyl groups, CH_2 and CH groups, in addition to the aromatic protons in the region 7.00–8.27 and the two broads signals corresponding to NH_2 and NH at 8.80 and 10.30 ppm. Structures **13** are preferable to **13'** on the basis of ^{1}H and ^{13}C NMR spectral data, besides our previous report on a similar work.[11,13] Thus, ^{1}H NMR spectrum of compound **13a**, as an example, showed signals at 6.97 (d, 2H), 7.09 (d, 1H), 7.23–7.25 (m, 1H), 7.37–7.49 (m, 5H), 7.66 (d, 2H), 7.89 (d, 1H), 8.21 (t, 1H) and 8.85 (brs, 2H). The ^{13}C NMR spectrum of **13b** showed an absorption band at 28.1 supporting one methyl group, signals between 107.4–160.0 corresponding to 22 nonequivalent sp^2 carbons and two signals supporting the presence of two carbonyl groups at 164.4 and 183.1 ppm. Moreover, the reaction mechanism may be proceeding as shown in Scheme 6. The 2-alkylthio derivatives **7a**,**b** underwent further alkylation at the N-3 nitrogen atom on treatment with alkyl iodide (in ethanolic sodium ethoxide solution) to afford 7-amino-3-alkyl-2-methylthio-5-(4-chlorophenyl)-6-(benzothiazol-2-yl)-pyrido[2,3-*d*]pyrimidin-4-ones **14a**,**b**.

Assignment of structures **14** to the dialkylated products is based on their spectral data. Besides, heating **7d** under reflux in a mixture of acetic anhydride and pyridine, led to cyclization and formation of 8-amino-2-acetyl-3-methyl-6-(4-chlorophenyl)-7-(benzothiazol-2-yl)-thiazolo-[4,5-*a*]pyrido[2,3-*d*]pyrimidin-5-one **15**, in good yield. The N-3 nitrogen atom was involved in the cyclization of **7d** to form **15**[15] and not the N-1 nitrogen atom. The IR spectrum of **15** displayed two carbonyl absorption bands at 1723 and 1686 cm^{-1}. Its ^{1}H NMR spectrum showed signals at 2.13 (s, 3H), 2.87 (s, 3H), 7.02 (d, 2H), 7.17 (d, 1H), 7.27 (t, 1H), 7.56–7.62 (m, 3H), 7.85 (d, 1H) and 8.58 (brs, 2H). Furthermore, ^{13}C NMR spectrum of **15** showed signals at 20.1 and 30.6 corresponding to the two methyl groups and 19 signals between 109.6–160.3 corresponding to 19 nonequivalent sp^2 carbons as well as two signals at 163.5 and 187.4 belonging to the two carbonyl groups. As an additional proof, compound **15** yielded 8-amino-2-cinnamoyl-3-methyl-7-(benzothiazol-2-yl)-thiazolo[4,5-*a*]pyrido[2,3-*d*]pyrimidin-5-one derivative **16** on heating with 4-methoxybenzaldehyde at 180 °C in the presence of a catalytic amount of piperidine.

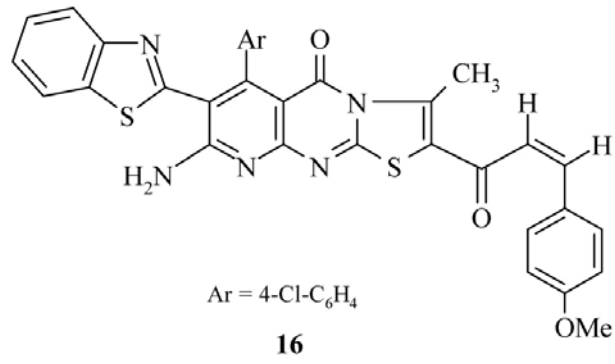


14



15

a: R = R^1 = CH$_3$; **b**: R = CH$_3$, R^1 = C$_2$H$_5$



Ar = 4-Cl-C$_6$H$_4$

16

The IR spectrum of **16** displayed two carbonyl absorption bands at 1708 and 1687 cm^{-1} which support the two carbonyl groups. The ^{1}H NMR spectrum of **16** showed two signals for the ethylenic protons (AB system) as *cis*-form (CH=CH) at 5.32 and 5.52 ppm as doublets (each for 1H) with J = 8.0 Hz. Moreover, in this case the *cis*-form is preferable than the *trans*-form due to steric hindrance in the structure.

3. Biological Results and Discussion

The investigation of antibacterial (Table 1) and antifungal (Table 2) screening data revealed that all the tested compounds **3–16** showed moderate to good inhibition at concentrations 1.56–25 μg mL^{-1} in dimethylsulfoxide. Compounds **3**, **4**, **5b**, **6b**, **7a**,**b**, **9a**, **13b** and **16** showed comparatively good activity against all the bacterial strains. Also compounds **4**, **7a**,**b**, **12a**, **13b** and **16** showed comparatively good activity against all the fungal strains. The good activity is attributed to the presence of pharmacologically active 1,3-benzothiazole, amino, thioxo, oxo and aryl groups attached to the pyrido[2,3-*d*]pyrimidine ring.

Table 1: Antimicrobial activity of some selected compounds synthesized

Compound	MIC in μg/mL, and zone of inhibition (mm)			
	F. flavus	*A. fumigatus*	*P. marneffei*	*T. mentagrophytes*
3	6.25 (16–20)	12 (11–15)	6.25 (16–20)	6.25 (16–20)
4	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
5a	6.25 (16–20)	12 (11–15)	12 (11–15)	12 (11–15)
5b	12 (11–15)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
6a	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	12 (11–15)
6b	6.25 (16–20)	12 (11–15)	6.25 (16–20)	6.25 (16–20)
7a	6.25 (16–20)	6.25 (16–20)	25 (<10)	6.25 (16–20)
7b	25 (<10)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
8	6.25 (16–20)	12 (11–15)	6.25 (16–20)	6.25 (16–20)
9a	6.25 (16–20)	6.25 (16–20)	12 (11–15)	12 (11–15)
10a	12 (11–15)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
12a	6.25 (16–20)	25 (<10)	6.25 (16–20)	6.25 (16–20)
12b	6.25 (16–20)	12 (11–15)	6.25 (16–20)	6.25 (16–20)
13a	12 (11–15)	6.25 (16–20)	6.25 (16–20)	12 (11–15)
13b	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
14a	6.25 (16–20)	12 (11–15)	12 (11–15)	6.25 (16–20)
15	12 (11–15)	6.25 (16–20)	6.25 (16–20)	12 (11–15)
16	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
Ciclopiroxolamine	3.125 (26–32)	6.25 (16–20)	6.25 (16–20)	3.125 (25–30)

Note: The MIC values were evaluated at concentration ranges, 1.56–25 μg/mL.

Table 2: Antifungal activity of some selected compounds synthesized

Compound	MIC in μg/mL, and zone of inhibition (mm)			
	F. flavus	*A. fumigatus*	*P. marneffei*	*T. mentagrophytes*
3	6.25 (16–20)	12 (11–15)	6.25 (16–20)	6.25 (16–20)
4	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
5a	6.25 (16–20)	12 (11–15)	12 (11–15)	12 (11–15)
5b	12 (11–15)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
6a	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	12 (11–15)
6b	6.25 (16–20)	12 (11–15)	6.25 (16–20)	6.25 (16–20)
7a	6.25 (16–20)	6.25 (16–20)	25 (<10)	6.25 (16–20)
7b	25 (<10)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
8	6.25 (16–20)	12 (11–15)	6.25 (16–20)	6.25 (16–20)
9a	6.25 (16–20)	6.25 (16–20)	12 (11–15)	12 (11–15)
10a	12 (11–15)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
12a	6.25 (16–20)	25 (<10)	6.25 (16–20)	6.25 (16–20)
12b	6.25 (16–20)	12 (11–15)	6.25 (16–20)	6.25 (16–20)
13a	12 (11–15)	6.25 (16–20)	6.25 (16–20)	12 (11–15)
13b	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
14a	6.25 (16–20)	12 (11–15)	12 (11–15)	6.25 (16–20)
15	12 (11–15)	6.25 (16–20)	6.25 (16–20)	12 (11–15)
16	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
Ciclopiroxolamine	3.125 (26–32)	6.25 (16–20)	6.25 (16–20)	3.125 (25–30)

Note: The MIC values were evaluated at concentration ranges, 1.56–25 μg/mL.

4. Conclusion

The research study reports the successful synthesis of a variety of fused and pendant heterocyclic systems from pyrido[2,3-*d*]pyrimidines and antimicrobial activity of the new synthesized systems bearing pyrido[2,3-*d*]pyrimidine moiety. The antimicrobial activity study revealed that all the compounds tested showed moderate to good antibacterial and antifungal activities against pathogenic strains.

5. Experimental

All melting points were measured on Electrothermal IA 9100 series digital melting point apparatus. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Jeol JNM-LA-400 FT NMR Spectrometer (Universität Konstanz, Germany) and a Jeol ECA500 MHz. Chemical shifts were expressed as δ values against $SiMe_4$ as internal standards. IR spectra were recorded as KBr pellets on a Nexus FT/IR

spectrometer Nicolet, USA (National Research Centre). Mass spectra were recorded on GCMS-QP 1000 EX Shimadzu, Japan. Microanalytical data were obtained by the Microanalytical Centre at Cairo University, Egypt. The starting materials **2**,[16] and hydrazonoyl chlorides **11a–c**[17,18] were prepared according to literature procedures. Biological activity screening was carried out in The Biotechnology and Fermentation Centre, Al-Azhar University, Cairo Egypt.

7-Amino-6-(benzothiazol-2-yl)-5-(4-chlorophenyl)-2,3-dihydro-2-thioxopyrido[2,3-*d*]pyrimidin-4*H*-one (3). A mixture of **2** (2.97 g, 0.01 mol) and 6-aminothiouracil **1** (1.43 g, 0.01 mol) was refluxed in 50 mL dimethylformamide for 20–25 h (TLC). The reaction mixture was allowed to cool. The deposited precipitate was filtered off, washed with ethanol and dried to produce **3** in good yield, as a yellow powder (dimethylformamide) in 75% yield, mp. 380–383 °C (dec.); IR (ν/cm^{-1}) 3366 (br, NH, NH_2), 3039 (CH aryl), 1691 (CO), 1640 (C=N). ^{1}H NMR (DMSO-d_6, δ, ppm) 7.16 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.23 (d, 1H, *J* = 8.1 Hz, Ar-H), 7.28 (d, 1H, *J* = 7.8 Hz, Ar-H), 7.31–7.34 (m, 1H, Ar-H), 7.45 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.94–7.99 (m, 1H, Ar-H), 8.20 (br, 2H), 10.30 (br, 1H), 11.53 (br, 1H) (NH_2, 2×NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6, δ, ppm) 100.3, 109.9, 121.4, 122.7, 125.5, 126.1, 127.8, 131.2, 133.4, 135.5, 135.6, 151.2, 152.0, 152.9, 157.9, 159.5 (sp^2 carbons) 163.4 (CO), 175.7 (CS); MS *m/z* 437 ([M$^+$], 100%). Anal. Calcd for $C_{20}H_{12}ClN_5OS_2$ (437.9): C, 54.85; H, 2.76; N, 15.99. Found: C, 54.81; H, 2.73; N, 15.84.

8-Amino-6-aryl-7-(benzothiazol-2-yl)-[1,3]thiazolo[4,5-*a*]pyrido[2,3-*d*]pyrimidine-3,5-dione (4). A mixture of **3** (4.37 g, 0.01 mol), chloroacetic acid (0.95 g, 0.01 mol) and anhydrous sodium acetate (1.64 g, 0.02 mol) was heated gently while stirring on a water bath (60 °C) for 2 h. The reaction mixture was allowed to cool to room temperature and poured into water (100 mL). The precipitate was filtered off. The compound was produced as a yellow powder (dioxane) in 63% yield, mp. 302–305 °C; IR (ν/cm^{-1}) 3360 (NH), 1687, 1674 (2CO), 1605 (C=N); ^{1}H NMR (DMSO-d_6, δ, ppm) 3.78 (s, 2H, CH_2), 7.23 (d, 2H, *J* = 8.3 Hz, Ar-H), 7.26 (d, 1H, *J* = 8.2 Hz, Ar-H), 7.30 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.34–7.37 (m, 1H, Ar-H), 7.70 (d, 2H, *J* = 8.4 Hz, Ar-H), 8.01–8.04 (m, 1H, Ar-H), 8.56 (brs, 2H, NH_2, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, δ, ppm) 56.87 (CH_3), 103.4, 109.9, 121.6, 122.7, 125.5, 126.1, 127.8, 128.3, 131.8, 133.4, 135.53, 135.56, 151.3, 152.0, 152.9, 157.9, 159.6 (sp^2 carbons), 163.4, 163.9 (2×CO); MS *m/z* 477 ([M$^+$], 100%). Anal. Calcd for $C_{22}H_{12}ClN_5O_2S_2$ (477.9): C, 55.28; H, 2.53; N, 14.65. Found: C, 55.32; H, 2.55; N, 14.70.

Preparation of compounds 5a–c. General Procedure: ***Method (A)***. A mixture of **3** (4.37 g, 0.01 mol), chloroacetic acid (0.95 g, 0.01 mol), the appropriate aromatic aldehyde (0.01 mol) and anhydrous sodium acetate (1.64 g, 0.02 mol) was stirred under reflux in 30 mL of glacial acetic acid and 15 mL of acetic anhydride for 15 h The reaction mixture was cooled and poured into cold water (100 mL). The deposited precipitate was filtered off and crystallized. ***Method (B)***. A mixture of **4** (4.78 g, 0.01 mol), aromatic aldehyde (0.01 mol) and anhydrous sodium acetate (1.64 g, 0.02 mol) was stirred under reflux in 30 mL of glacial acetic acid and 15 mL of acetic anhydride for 5 h. The reaction mixture was allowed to cool to room temperature, poured into cold water (100 mL). The precipitate was filtered off and crystallized to produce **5a–c**.

8-Amino-2-(4-chlorophenylmethylene)-6-(4-chlorophenyl)-7-(benzothiazol-2-yl)-thiazolo[4,5-*a*]pyrido[2,3-*d*]pyrimidine-3,5-dione (5a). It was obtained from **3** (4.37 g, 0.01 mol) and 4-chlorobenzaldehyde (1.41 g, 0.01 mol) as yellow powder (dimethylformamide) in 75% yield, mp. 321–323 °C; IR (ν/cm^{-1}) 3350 (NH), 1685, 1678 (2×CO), 1620 (C=N); ^{1}H NMR (DMSO-d_6, δ, ppm) 7.23 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.26 (d, 1H, *J* = 7.9 Hz, Ar-H), 7.29–7.31 (2×d, 3H, Ar-H), 7.36 (t, 1H, *J* = 6.1 Hz, Ar-H), 7.68 (d, 2H, *J* = 8.4 Hz, Ar-H), 8.03 (d, 1H, *J* = 7.7 Hz, Ar-H), 8.28 (d, 2H, *J* = 8.3 Hz, Ar-H), 8.51 (s, 1H, methylenic), 8.76 (brs, 2H, NH_2, D_2O exchangeable); MS *m/z* 600 ([M$^+$], 100%), 601 ([M$^+$+1], 38%), 602 ([M$^+$+2], 33%). Anal. Calcd for $C_{29}H_{15}Cl_2N_5O_2S_2$ (600.5): C, 58.00; H, 2.52; N, 11.66. Found: C, 57.89; H, 2.60; N, 11.69.

8-Amino-2-(4-methoxyphenylene)-6-(4-chlorophenyl)-7-(benzothiazol-2-yl)-thiazolo[4,5-*a*]pyrido[2,3-*d*]pyrimidine-3,5-dione (5b). It was obtained from **3** (4.37 g, 0.01 mol) and 4-anisaldehyde (1.36 g, 0.01 mol), as white powder (dioxane) in 76% yield, mp. 318–321 °C; IR (ν/cm^{-1}) 3420 (NH), 1686, 1677 (2×CO), 1610 (C=N); ^{1}H NMR (DMSO-d_6, δ, ppm) 4.02 (s, 3H, OCH_3), 7.21 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.26 (d, 1H, *J* = 8.1 Hz, Ar-H), 7.31 (m, 3H, Ar-H), 7.34–7.36 (m, 1H, Ar-H), 7.63 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.98 (d, 1H, *J* = 8.1 Hz, Ar-H), 8.26 (d, 2H, *J* = 8.3 Hz, Ar-H), 8.53 (s, 1H, methylenic), 8.75 (brs, 2H, NH_2, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, δ, ppm) 55.4 (CH_3), 100.3, 108.7, 120.5, 121.6, 123.7, 125.4, 126.2, 127.5, 127.9, 128.3, 128.7, 129.1, 131.2, 133.5, 135.56, 135.66, 143.7, 148.2, 151.1, 152.1, 152.6, 157.7, 159.3 (sp^2 carbons), 162.7, 163.9 (2×CO); MS *m/z* 596 ([M$^+$], 100%), 597 ([M$^+$+1], 34%). Anal. Calcd for $C_{30}H_{18}ClN_5O_3S_2$ (596.1): C, 60.45; H, 3.04; N, 11.75. Found: C, 60.48; H, 2.99; N, 11.83.

8-Amino-2-(4-tollylmethylene)-6-(4-chlorophenyl)-7-(benzothiazol-2-yl)-thiazolo-[4,5-*a*]pyrido[2,3-*d*]pyrimidine-3,5-dione (5c). It was obtained from **3** (4.37 g, 0.01 mol) and 4-toluylaldehyde (1.20 g, 0.01 mol) as

yellow powder (dimethylformamide) in 80% yield, mp. 298–301 °C; IR (ν/cm^{-1}) 3335 (NH), 1690, 1678 (2×CO), 1630 (C=N); ^{1}H NMR (DMSO-d_6, δ, ppm) 2.31 (s, 3H, CH_3), 7.22 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.28 (d, 1H, *J* = 7.8 Hz, Ar-H), 7.32 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.36–7.40 (m, 2H, Ar-H), 7.61 (d, 2H, *J* = 8.4 Hz, Ar-H), 8.27 (d, 2H, *J* = 8.3 Hz, Ar-H), 8.50 (s, 1H, methylenic), 8.81 (brs, 2H, NH_2, D_2O exchangeable). Anal. Calcd for $C_{30}H_{18}ClN_5O_2S_2$ (580.1): C, 62.12; H, 3.13; N, 12.07. Found: C, 62.09; H, 3.17; N, 12.11.

Preparation of compounds 6a,b. General Procedure. A mixture of **5a**,**b** (0.01 mol), hydroxylamine hydrochloride (0.70 g, 0.01 mol) and anhydrous sodium acetate (1.64 g, 0.02 mol) was stirred under reflux in 30 mL glacial acetic acid 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 and dried to produce **6a**,**b**.

7-Amino-3,9-di(4-chlorophenyl)-8-(benzothiazol-2-yl)-isoxazolo[5´,4´:4,5]thiazolo[3,2-*a*]pyrido[2,3-*d*]pyrimidin-11-one (6a). It was obtained from **5a** (6.00 g, 0.01 mol) as green crystals (*n*-hexane) in 61% yield, mp. 341–344 °C (dec.); IR (ν/cm^{-1}) 3350 (br, NH), 3380 (NH), 1687 (CO), 1640 (C=N); ^{1}H NMR (DMSO-d_6, δ, ppm) 6.04 (d, 1H, *J* = 6.4 Hz, isoxazole), 7.20 (d, 2H, *J* = 8.3 Hz, Ar-H), 7.25 (d, 1H, *J* = 7.9 Hz, Ar-H), 7.29–7.32 (2×d, 3H, Ar-H), 7.36 (t, 1H, *J* = 6.5 Hz, Ar-H), 7.57 (d, 2H, *J* = 8.4 Hz, Ar-H), 8.03 (d, 1H, *J* = 8.2 Hz, Ar-H), 8.30 (d, 2H, *J* = 8.4 Hz, Ar-H), 8.64 (brs, 2H, NH_2, D_2O exchangeable), 10.22 (brs, 1H, NH, D_2O exchangeable); MS *m/z* 615 ([M$^+$], 100%), 616 ([M$^+$+1], 31%), 617 ([M$^+$+2], 26%). Anal. Calcd for $C_{29}H_{16}Cl_2N_6O_2S_2$ (615.5): C, 56.58; H, 2.62; N, 13.65. Found: C, 56.53; H, 2.59; N, 13.74.

7-Amino-9-(4-chlorophenyl)-3-(4-methoxyphenyl)-8-(benzothiazol-2-yl)-isoxazolo[5´,4´:4,5]thiazolo[3,2-*a*]pyrido[2,3-*d*]pyrimidin-11-one (6b). It was obtained from **5b** (5.96 g, 0.01 mol) as a yellow powder (*n*-hexane) in 63% yield, mp. 332–335 °C (dec.); IR (ν/cm^{-1}) 3380 (br, NH), 3053 (CH aryl), 2918 (CH alkyl), 1685 (CO), 1616 (C=N); ^{1}H NMR (DMSO-d_6, δ, ppm) 3.96 (s, 3H, OCH_3), 6.02 (d, 1H, *J* = 6.3 Hz, isoxazole), 7.23 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.27 (d, 1H, *J* = 7.8 Hz, Ar-H), 7.30–7.33 (2×d, 3H, Ar-H), 7.36–7.39 (m, 1H, Ar-H), 7.60 (d, 2H, *J* = 8.4 Hz, Ar-H), 8.02 (d, 1H, *J* = 7.7 Hz, Ar-H), 8.30 (d, 2H, *J* = 8.4 Hz, Ar-H), 8.68 (brs, 2H, NH_2, D_2O exchangeable), 9.80 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, δ, ppm) 55.5 (CH_3), 70.7 (C-3 isoxazole), 101.3, 107.9, 119.6, 121.5, 122.7, 124.4, 126.2, 127.6, 128.4, 128.7, 129.3, 131.3, 133.4, 135.5, 135.9, 142.7, 145.1, 148.1, 151.0, 152.1, 152.7, 157.5, 159.3 (sp^2 carbons), 163.9 (CO); MS *m/z* 611 ([M$^+$], 100%). Anal. Calcd for $C_{30}H_{19}ClN_6O_3S_2$ (611.1): C, 58.96; H, 3.13; N, 13.75. Found: C, 59.00; H, 3.18; N, 13.88.

Preparation of compounds 7a–d. General procedure. To a warmed ethanolic KOH solution (prepared by dissolving 0.56 g (0.01 mol) of KOH in 50 mL of ethanol) compound **3** (4.37 g, 0.01 mol) was added, the heating was continued for 30 min, the mixture was allowed to cool to room temperature and a proper halo-compound (0.012 mol) was added. The mixture was stirred under reflux for 5 h, then cooled to the room temperature and poured into cold water (100 mL). The solid product precipitated was filtered off, washed with 100 mL water and dried to produce **7a**–**d**.

7-Amino-2-(methylthio)-5-(4-chlorophenyl)-6-(benzothiazol-2-yl)-pyrido[2,3-*d*]pyrimidin-4(4*H*)-one (7a). It was obtained from **3** (4.37 g, 0.01 mol) and methyl iodide (1.70 g, 0.012 mol) as pale yellow crystals (dioxane) in 82% yield, mp. 289–291 °C; IR (ν/cm^{-1}) 3403 (br, NH), 3036 (CH aryl), 2925 (CH alkyl), 1687 (CO), 1652 (C=N); ^{1}H NMR (DMSO-d_6, δ, ppm) 2.86 (s, 3H, CH_3), 7.16 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.23 (d, 1H, *J* = 7.7 Hz, Ar-H), 7.29 (d, 1H, *J* = 7.8 Hz, Ar-H), 7.32–7.35 (m, 1H, Ar-H), 7.47 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.92–7.97 (m, 1H, Ar-H), 8.53 (br, 2H), 11.20 (br, 1H) (NH_2, NH, D_2O exchangeable). Anal. Calcd for $C_{21}H_{14}ClN_5OS_2$ (451.9): C, 55.81; H, 3.12; N, 15.49. Found: C, 55.83; H, 3.07; N, 15.53.

7-Amino-2-(ethylthio)-5-(4-chlorophenyl)-6-(benzothiazol-2yl)-pyrido[2,3-*d*]pyrimidin-4(4*H*)-one (7b). It was obtained from **3** (4.37 g, 0.01 mol) and ethyl iodide (1.87 g, 0.012 mol) as orange crystals (dioxane) in 83% yield, mp. 247–250 °C; IR (ν/cm^{-1}) 3420 (br, NH), 3061 (CH aryl), 2906 (CH alkyl), 1684 (CO), 1635 (C=N); ^{1}H NMR (DMSO-d_6, δ, ppm) 1.37 (t, 3H, *J* = 6.8 Hz, CH_3), 2.86 (t, 2H, *J* = 6.9 Hz, CH_2), 7.19 (d, 2H, *J* = 8.2 Hz, Ar-H), 7.24 (d, 1H, *J* = 7.8 Hz, Ar-H), 7.31 (d, 1H, *J* = 7.9 Hz, Ar-H), 7.36–7.38 (m, 1H, Ar-H), 7.57 (d, 2H, *J* = 8.3 Hz, Ar-H), 8.01–8.85 (m, 1H, Ar-H), 8.75 (br, 2H), 10.65 (br, 1H) (NH_2, NH). Anal. Calcd for $C_{22}H_{16}ClN_5OS_2$ (465.9): C, 56.70; H, 3.46; N, 15.03. Found: C, 56.65; H, 3.51; N, 14.94.

7-Amino-2-[*S*-(*N*-4-chlorophenylacetamido)]-5-(4-chlorophenyl)-6-(benzothiazol-2-yl)-pyrido[2,3-*d*]pyrimidin-4(4*H*)-one (7c). It was obtained from **3** (4.37 g, 0.01 mol) and 2-chloroacetanilide (1.69 g, 0.01 mol) as yellow crystals (dioxane) in 80% yield, mp. 360–363 °C (dec.); IR (ν/cm^{-1}) 3400 (br, NH), 3021 (CH aryl), 2920 (CH alkyl), 1689, 1676 (2×CO), 1609 (C=N); ^{1}H NMR (DMSO-d_6, δ, ppm) 2.75 (s, 2H, CH_2), 6.95–7.05 (2×d, 4H, Ar-H), 7.20 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.40 (d, 1H, *J* = 7.9 Hz, Ar-H), 7.55–7.65 (m, 3H, Ar-H), 7.75–7.85 (m, 1H, Ar-H), 8.03 (d, 2H, *J* = 8.5 Hz, Ar-H), 8.74 (brs, 2H), 9.50 (brs, 1H), 12.10 (brs, 1H) (NH_2, 2×NH, D_2O exchangeable); MS *m/z* 605 ([M$^+$], 56%), 571 ([M$^+$+1–Cl], 11%), 451 ([M$^+$+2–CONHC$_6$H$_4$Cl], 22%). Anal. Calcd for

$C_{28}H_{18}Cl_2N_6O_2S_2$ (605.5): C, 55.54; H, 2.99; N, 13.88. Found: C, 55.60; H, 3.02; N, 14.00.

7-Amino-2-(acetylacetonethio)-5-(4-chlorophenyl)-6-(benzothiozol-2-yl)-pyrido[2,3-*d*]pyrimidin-4(4*H*)-one (7d). It was obtained from **3** (4.37 g, 0.01 mol) and 3-chloro-2,4-pentanedione (1.61 g, 0.012 mol) as yellow crystals (dioxane) in 87% yield, mp. 280–283 °C; IR (ν/cm^{-1}) 3420 (br, NH), 3052 (CH aryl), 2928 (CH alkyl), 1718, 1712, 1676 (3×CO), 1625 (C=N); ^{1}H NMR (DMSO-d_6, δ, ppm) 3.04 (s, 3H, $COCH_3$), 3.06 (s, 3H, $COCH_3$), 3.97 (s, 1H, CH), 7.14 (d, 2H, *J* = 8.3 Hz, Ar-H), 7.23 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.29 (d, 1H, *J* = 7.8 Hz, Ar-H), 7.33–7.37 (m, 1H, Ar-H), 7.43 (d, 2H, *J* = 8.3 Hz, Ar-H), 7.98–8.02 (m, 1H, Ar-H), 8.75 (br, 2H), 10.30 (br, 1H) (NH_2, NH, D_2O exchangeable); MS *m/z* 536 ([M$^+$], 100%), 493 ([M$^+$–$COCH_3$], 44%), 438 ([M$^+$+1–CH($COCH_3$)$_2$], 85%), 406 ([M$^+$+1–SCH($COCH_3$)], 19%). Anal. Calcd for $C_{25}H_{18}ClN_5O_3S_2$ (536.0): C, 56.02; H, 3.38; N, 13.07. Found: C, 56.11; H, 3.40; N, 13.13.

7-Amino-5-(4-chlorophenyl)-2-hydrazino-6-(benzothiazol-2-yl)-pyrido[2,3-*d*]pyrimidin-4(4*H*)-one (8). A suspension of **7a** or **7b** (0.01 mol) in hydrazine hydrate (99–100%) (25 mL) was stirred under reflux in 100 mL of ethanol for 8 h. The reaction mixture was allowed to cool to room temperature. The solid which separated, was filtered, washed with ethanol and dried to produced **8** (dimethylformamide) in 89% yield, mp. 372–375 °C (dec.); IR (ν/cm^{-1}) 3410 (br, NH), 3042 (CH aryl), 2918 (CH alkyl), 1682 (CO), 1624 (C=N); ^{1}H NMR (DMSO-d_6, δ, ppm) 3.50 (brs, 2H, NH_2), 7.20 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.28–7.29 (m, 1H, Ar-H), 7.31–7.34 (m, 1H, Ar-H), 7.40 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.86 (d, 1H, *J* = 7.8 Hz, Ar-H), 8.25 (br, 3H), 11.20 (br, 1H), 12.10 (br, 1H) (2×NH_2, 2×NH, D_2O exchangeable); MS *m/z* 435 ([M$^+$], 100%), 436 ([M$^+$ +1], 26%). Anal. Calcd for $C_{20}H_{14}ClN_7OS$ (435.9): C, 55.12; H, 3.24; N, 22.49. Found: C, 55.15; H, 3.27; N, 22.52.

Preparation of compounds 9a,b. General procedure. To a warmed ethanolic KOH solution (prepared by dissolving 0.56 g (0.01 mol) of KOH in 50 mL of ethanol) compound **3** (4.37 g, 0.01 mol) was added, the heating was continued for 30 min and the mixture was allowed to cool to room temperature, and a proper halo-ketone (0.012 mol) was added. The mixture was stirred under reflux for 5 h, then cooled to the room temperature and poured into cold water (100 mL). The solid product precipitated was filtered off, washed with 100 mL water and dried to produce **9a**,**b**.

7-Amino-2-(*S*-acetone)-5-(4-chlorophenyl)-6-(benzothiazol-2-yl)-pyrido[2,3-*d*]pyrimidin-4(4*H*)-one (**9a**). It was obtained from **3** (4.37 g, 0.01 mol) and chloroacetone (1.15 g, 0.012 mol) as yellow crystals (ethanol) in 68% yield, mp. 272–274 °C; IR (ν/cm^{-1}) 3400 (br, NH), 3034 (CH aryl), 2919 (CH alkyl), 1715, 1685 (2×CO), 1620 (C=N); ^{1}H NMR (DMSO-d_6, δ, ppm) 1.75 (s, 3H, CH_3), 4.28 (s, 2H, CH_2), 7.00 (d, 2H, *J* = 8.2 Hz, Ar-H), 7.20 (d, 1H, *J* = 7.9 Hz, Ar-H), 7.28–7.29 (m, 1H, Ar-H), 7.55–7.63 (m, 3H, Ar-H), 7.86 (d, 1H, *J* = 7.7 Hz, Ar-H), 8.90 (brs, 2H), 10.30 (brs, 1H) (NH_2, NH, D_2O exchangeable); MS *m/z* 493 ([M$^+$], 22%), 492 ([M$^+$–H], 37%), 451 ([M$^+$+1–$COCH_3$], 100%), 436 ([M$^+$–CH_2COCH_3], 66%), 404 ([M$^+$–SCH_2CO-CH_3], 28%). Anal. Calcd for $C_{23}H_{16}ClN_5O_2S_2$ (493.9): C, 55/92; H, 3.264; N, 14.18. Found: C, 54.00; H, 3.19; N, 14.12.

7-Amino-2-(*S*-phenacyl)-5-(4-chlorophenyl)-6-(benzothiazol-2-yl)-pyrido[2,3-*d*]pyrimidin-4(4*H*)-one (**9b**). It was obtained from **3** (4.37 g, 0.01 mol) and phenacyl bromide (1.99 g, 0.01 mol) as pale yellow crystals (ethanol) in 71% yield, mp. 292–294 °C; IR (ν/cm^{-1}) 3430 (br, NH), 3029 (CH aryl), 2907 (CH alkyl), 1720, 1683 (2×CO), 1642 (C=N); ^{1}H NMR (DMSO-d_6, δ, ppm) 4.80 (s, 2H, CH_2), 7.00 (d, 2H, *J* = 8.3 Hz, Ar-H), 7.20 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.45–7.75 (m, 5H, Ar-H), 8.10–8.15 (m, 3H, Ar-H), 8.36 (d, 2H, *J* = 8.5 Hz, Ar-H), 8.85 (brs, 2H), 11.50 (brs, 1H) (NH_2, NH, D_2O exchangeable); MS *m/z* 556 ([M$^+$], 100%). Anal. Calcd for $C_{28}H_{18}ClN_5O_2S_2$ (556.0): C, 60.48; H, 3.26; N, 12.59. Found: C, 60.45; H, 3.30; N, 12.61.

Preparation of compounds 10a,b. General procedure. A solution of **9a**,**b** (0.01 mol) in glacial acetic acid (40 mL) and catalytic amount of sulphuric acid (2 mL) was stirred under reflux for 12 h. The reaction mixture was allowed to cool, poured into cold water (100 mL), neutralized by ammonia solution; the solid precipitate was filtered off, washed with water and crystallized to produce **10a**,**b**.

8-Amino-6-(4-chlorophenyl)-7-(benzothiazol-2-yl)-3-methyl-1,2-dihydro-5*H*-thiazolo[4,5-*a*]pyrido[2,3-*d*]pyrimidin-5-one (10a). It was obtained from **9a** (4.82 g, 0.01 mol) as yellow crystals (ethanol) in 63% yield, mp. 328–331 °C; IR (ν/cm^{-1}) 3390 (NH), 3034 (CH aryl), 2908 (CH alkyl), 1690 (CO), 1620 (C=N); ^{1}H NMR (DMSO-d_6, δ, ppm) 2.11 (s, 3H, CH_3), 7.02 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.16 (d, 1H, *J* = 7.7 Hz, Ar-H), 7.26–7.29 (m, 1H, Ar-H), 7.50–7.62 (m, 3H, Ar-H), 7.83 (d, 1H, *J* = 7.8 Hz, Ar-H), 8.20 (s, 1H, thiazole), 8.68 (brs, 2H, NH_2, D_2O exchangeable); MS *m/z* 475 ([M$^+$], 100%), 460 ([M$^+$–CH_3], 37%). Anal. Calcd for $C_{23}H_{14}ClN_5OS_2$ (475.9): C, 58.04; H, 2.96; N, 14.71. Found: C, 58.10; H, 3.01; N, 14.74.

8-Amino-6-(4-chlorophenyl)-7-(benzothiazol-2-yl)-3-phenyl-*H*-1,2-dihydro-5*H*-thiazolo[4,5-*a*]pyrido[2,3-*d*]pyrimidin-5-one (10b). It was obtained from **9b** (5.56 g, 0.01 mol) as yellow crystals (dioxane) in 66% yield, mp. 341–343 °C (dec.); IR (ν/cm^{-1}) 3375 (NH), 3030 (CH

aryl), 2923 (CH alkyl), 1686 (CO), 1625 (C=N); ^{1}H NMR (DMSO-d_6, δ, ppm) 6.97 (d, 2H, J = 8.3 Hz, Ar-H), 7.13 (d, 1H, J = 7.8 Hz, Ar-H), 7.40–7.78 (m, 5H, Ar-H), 8.00–8.12 (m, 3H, Ar-H), 8.33 (d, 2H, J = 8.3 Hz, Ar-H), 8.41 (s, 1H, thiazole proton), 8.92 (brs, 2H, NH_2, D_2O exchangeable); MS *m/z* 538 ([M^+], 100%), 461 ([M^+–C_6H_5], 68%). Anal. Calcd for $C_{28}H_{16}ClN_5OS_2$ (538.0): C, 62.50; H, 2.99; N, 13.02. Found: C, 62.46; H, 3.02; N, 13.09.

Preparation of compounds 12a–c. **General Procedure.** A suspension of **3** (4.37 g, 0.01 mol) and hydrazonoyl chlorides **11a–c** (0.01 mol) in dry chloroform (30 mL) was stirred under reflux for 5 h. The deposited precipitate was filtered off, washed with 30 mL chloroform, dried and crystallized to produce **12a–c**.

7-Amino-2-[*S*-(*N*-phenyl-1-phenylazo)]-5-(4-chlorophenyl)-6-(benzothiazol-2-yl)-pyrido[2,3-*d*]pyrimidin-4(4*H*)-one (**12a**). It was obtained from *N*-phenylbenzenecarbohydrazonoyl chloride **11a** (2.31 g, 0.01 mol) as yellow crystals (dioxane) in 68% yield, mp. 301–303 °C; IR (ν/cm^{-1}) 3385 (NH), 3052 (CH aryl), 2929 (CH alkyl), 1692 (CO), 1622 (C=N); ^{1}H NMR (DMSO-d_6, δ, ppm) 4.54 (s, 1H, CH), 6.94 (d, 2H, J = 8.5 Hz, Ar-H), 7.00 (d, 1H, J = 7.6 Hz, Ar-H), 7.20–7.22 (m, 6H, Ar-H), 7.40–7.48 (m, 5H, Ar-H), 7.62 (d, 2H, J = 8.5 Hz, Ar-H), 7.71 (d, 1H, J = 7.6 Hz, Ar-H), 8.24 (t, 1H, J = 6.4 Hz, Ar-H), 8.70 (brs, 2H), 10.50 (brs, 1H) (NH_2, NH, D_2O exchangeable). Anal. Calcd for $C_{33}H_{22}ClN_7OS_2$ (632.1): C, 62.69; H, 3.51; N, 15.51. Found: C, 62.71; H, 3.47; N, 15.53.

7-Amino-2-[*S*-(acetonyl-1-(4-chlorophenylazo))]-5-(4-chlorophenyl)-6-(benzothiazol-2-yl)-pyrido[2,3-*d*]pyrimidin-4(4*H*)-one (**12b**). It was obtained from 2-oxo-*N*-(4-chlorophenyl)propane hydrazonoyl chloride **11b** (1.96 g, 0.01 mol) as pale yellow crystals (ethanol) in 65% yield, mp. 168–171 °C; IR (ν/cm^{-1}) 3400 (br, NH), 3032 (CH aryl), 2903 (CH alkyl), 1730, 1683 (2×CO), 1634 (C=N); ^{1}H NMR (DMSO-d_6, δ, ppm) 2.74 (s, 3H, CH_3), 4.52 (s, 1H, CH), 6.97–7.06 (m, 4H, Ar-H), 7.16 (d, 1H, J = 7.9 Hz, Ar-H), 7.31 (t, 1H, J = 6.3 Hz, Ar-H), 7.72 (d, 2H, J = 8.2 Hz, Ar-H), 7.93 (t, 1H, J = 6.2 Hz, Ar-H), 8.03 (d, 1H, J = 8.0 Hz, Ar-H), 8.24 (d, 2H, J = 8.4 Hz, Ar-H), 8.68 (brs, 2H), 10.10 (brs, 1H) (NH_2, NH, D_2O exchangeable); MS *m/z* 632 ([M^+], 100%), 633 ([M^++1], 29%). Anal. Calcd for $C_{29}H_{19}Cl_2N_7O_2S_2$ (632.5): C, 55.06; H, 3.03; N, 15.50. Found: C, 55.02; H, 3.00; N, 15.47.

7-Amino-2-[*S*-(ethylcarboxylate-1-tollylazo)]-5-(4-chlorophenyl)-6-(benzothiazol-2-yl)-pyrido[2,3-*d*]pyrimidin-4(4*H*)-one (**12c**). It was obtained from chloro-(4-tolylhydrazono)ethyl acetate **11c** (2.42 g, 0.01 mol) as pale brown crystals (dioxane) in 69% yield, mp. 245–248 °C; IR (ν/cm^{-1}) 3408 (br, NH), 3034 (CH aryl), 2927 (CH alkyl), 1726, 1685 (2×CO), 1632 (C=N); ^{1}H NMR (DMSO-d_6, δ, ppm) 1.29 (t, 3H, J = 7.0 Hz, CH_3), 2.78 (s, 3H, CH_3), 4.19 (q, 2H, J = 7.0 Hz, CH_2), 4.42 (s, 1H, CH), 7.00–7.06 (2×d overlapped, 4H, Ar-H), 7.14 (d, 1H, J = 7.6 Hz, Ar-H), 7.32 (t, 1H, J = 6.4 Hz, Ar-H), 7.73 (d, 2H, J = 8.5 Hz, Ar-H), 7.92 (t, 1H, J = 6.2 Hz, Ar-H), 8.02–8.05 (m, 1H, Ar-H), 8.24 (d, 2H, J = 8.5 Hz, Ar-H), 8.80 (brs, 2H), 10.30 (brs, 1H) (NH_2, NH, D_2O exchangeable); MS *m/z* 642 ([M^+], 30%), 643 ([M^++1], 27%). Anal. Calcd for $C_{31}H_{24}ClN_7O_4S_2$ (642.1): C, 57.98; H, 3.77; N, 15.27. Found: C, 57.89; H, 3.73; N, 15.17.

Preparation of compounds 13a–c. General Procedure. A mixture of **3** (4.37 g, 0.01 mol) and hydrazonoyl chlorides **11a–c** (0.01 mol) was stirred under reflux in dry chloroform (30 mL) with 4 drops of triethylamine for 12 h. The solvent was evaporated under reduced pressure. The solid produced was washed three times by 30 mL of methanol and crystallized to produce **13a–c**.

8-Amino-*N*1,3-diphenyl-6-(4-chlorophenyl)-7-(benzothiazol-2-yl)-pyrido[2,3-*d*][1,2,4]triazolo[4,5-*a*]pyrimidin-5-one (13a). It was obtained from *N*-phenylbenzenecarbohydrazonoyl chloride **11a** (2.31 g, 0.01 mol) as white crystals (dimethylformamide) in 70% yield, mp. 311–313 °C; IR (ν/cm^{-1}) 3395 (NH), 3045 (CH aryl), 2917 (CH alkyl), 1696 (CO), 1643 (C=N); ^{1}H NMR (DMSO-d_6, δ, ppm) 6.97 (d, 2H, J = 8.5 Hz, Ar-H), 7.09 (d, 1H, J = 7.9 Hz, Ar-H), 7.23–7.25 (m, 6H, Ar-H), 7.37–7.49 (m, 5H, Ar-H), 7.66 (d, 2H, J = 8.4 Hz, Ar-H), 7.89 (d, 1H, J = 8.0 Hz, Ar-H), 8.21 (t, 1H, J = 6.6 Hz, Ar-H), 8.85 (brs, 2H, NH_2, D_2O exchangeable). Anal. Calcd for $C_{33}H_{20}ClN_7OS$ (598.0): C, 66.27; H, 3.37; N, 16.39. Found: C, 66.21; H, 3.34; N, 16.42.

8-Amino-3-acetyl-*N*1-(4-chlorophenyl)-6-(4-chlorophenyl)-7-(benzothiazol-2-yl)pyrido[2,3-*d*][1,2,4]triazolo[4,5-*a*]pyrimidin-5-one (13b). It was obtained from 2-oxo-*N*-(4-chlorophenyl)propane hydrazonoyl chloride **11b** (1.96 g, 0.01 mol) as yellow powder (dimethylformamide) in 72% yield, mp. 324–326 °C; IR (ν/cm^{-1}) 3360 (NH), 2998 (CH aryl), 2924 (CH alkyl), 1749, 1696 (2×CO), 1668 (C=N); ^{1}H NMR (DMSO-d_6, δ, ppm) 2.86 (s, 3H, CH_3), 6.95 (d, 2H, J = 8.4 Hz, Ar-H), 7.08 (d, 2H, J = 8.5 Hz, Ar-H), 7.19 (d, 1H, J = 7.7 Hz, Ar-H), 7.27 (t, 1H, J = 6.5 Hz, Ar-H), 7.68 (d, 2H, J = 8.3 Hz, Ar-H), 7.90–7.93 (m, 1H, Ar-H), 8.02 (t, 1H, J = 6.2 Hz, Ar-H), 8.21 (d, 2H, J = 8.4 Hz, Ar-H), 8.64 (brs, 2H, NH_2); ^{13}C NMR (DMSO-d_6, δ, ppm) 28.1 (CH_3), 107.4, 113.5, 114.5, 122.0, 126.4, 128.8, 129.30, 129.37, 130.2, 130.9, 131.3, 134.9, 135.5, 138.4, 141.5, 143.3, 146.2, 149.0, 155.1, 158.3, 159.1, 160.0 (sp^2 carbons), 164.4, 183.1 (2×CO); MS *m/z* 598 ([M^+], 100%), 599 ([M^++1], 27%), 600 ([M^++2], 18%). Anal. Calcd for $C_{29}H_{17}Cl_2N_7O_2S$ (598.4): C, 58.20; H, 2.86; N, 16.38. Found: C, 58.23; H, 2.85; N, 16.40.

8-Amino-3-acetyl-*N*1-(4-chlorophenyl)-6-(4-chlorophenyl)-7-(benzothiazol-2-yl)pyrido[2,3-*d*][1,2,4]triazolo[4,5-*a*]pyrimidin-5-one (13c). It was obtained from chloro(4-tolylhydrazono)ethylacetate **11c** (2.41 g, 0.01 mol) as white crystals (dimethylformamide) in 65% yield, mp. 278–281 °C; IR (ν/cm^{-1}) 3400 (NH), 3036 (CH aryl), 2920 (CH alkyl), 1747, 1700 (2×CO), 1619 (C=N); ^{1}H NMR (DMSO-d_6, δ, ppm) 1.26 (t, 3H, *J* = 7.0 Hz, CH_3), 2.75 (s, 3H, CH_3), 4.12 (q, 2H, *J* = 7.0 Hz, CH_2), 6.98 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.04 (d, 2H, *J* = 8.3 Hz, Ar-H), 7.16 (d, 1H, *J* = 7.9 Hz, Ar-H), 7.28–7.32 (m, 1H, Ar-H), 7.70 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.94 (t, 1H, *J* = 6.0 Hz, Ar-H), 8.14 (d, 1H, *J* = 7.6 Hz, Ar-H), 8.24 (d, 2H, *J* = 8.4 Hz, Ar-H), 8.60 (brs, 2H, NH_2, D_2O exchangeable); MS *m/z* 608 ([M$^+$], 100%), 609 ([M$^+$+1], 30%). Anal. Calcd for $C_{31}H_{22}ClN_7O_3S$ (608.0): C, 61.23; H, 3.65; N, 16.12. Found: C, 61.18; H, 3.50; N, 16.13.

Preparation of compounds 14a,b. General Procedure. To a warmed ethanolic sodium ethoxide solution (prepared by dissolving 0.23 g (0.01 mol) of sodium metal in 30 mL of ethanol) compound **7a** (4.52 g, 0.01 mol) was added , the heating was continued for 30 min, the mixture was allowed to cool to room temperature and the proper alkyliodide (0.012 mol) was added. The mixture was stirred under reflux for 3 h, cooled to room temperature and poured into cold water (100 mL). The solid precipitated was filtered off, washed with water and dried to produce **14a**,**b** in high yields.

7-Amino-3-methyl-2-methylthio-5-(4-chlorophenyl)-6-(benzothiazol-2-yl)pyrido[2,3-*d*]pyrimidin-4(4*H*)-one (14a). It was obtained from methyl iodide (1.72 g, 0.012 mol) as yellow crystals (benzene) in 84% yield, mp. 276–279 °C; IR (ν/cm^{-1}) 3385 (NH), 3065 (CH aryl), 2930 (CH alkyl), 1699 (CO), 1650 (C=N); ^{1}H NMR (DMSO-d_6, δ, ppm) 2.86 (s, 3H, SCH_3), 3.98 (s, 3H, N-CH_3), 7.04 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.16 (d, 1H, *J* = 7.9 Hz, Ar-H), 7.31–7.35 (m, 1H, Ar-H), 7.73 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.90–7.95 (m, 1H, Ar-H), 8.02 (d, 1H, *J* = 7.7 Hz, Ar-H), 8.59 (brs, 2H, NH_2, D_2O exchangeable); MS *m/z* 465 ([M$^+$], 100%), 418 ([M$^+$–SCH_3], 56%). Anal. Calcd for $C_{22}H_{16}ClN_5OS_2$ (465.9): C, 56.70; H, 3.46; N, 15.03. Found: C, 56.65; H, 3.48; N, 15.09.

7-Amino-3-ethyl-2-methylthio-5-(4-chlorophenyl)-6-(benzothiazol-2-yl)-pyrido[2,3-*d*]pyrimidin-4(4*H*)-one (14b). It was obtained from ethyl iodide (1.86 g, 0.012 mol) as yellow powder (dioxane) in 76%, mp. 251–263 °C; IR (ν/cm^{-1}) 3410 (NH), 3045 (CH aryl), 2914 (CH alkyl), 1700 (CO), 1635 (C=N); ^{1}H NMR (DMSO-d_6, δ, ppm) 1.32 (t, 3H, *J* = 7.0 Hz, CH_3), 2.94 (s, 3H, SCH_3), 4.36 (q, 2H, *J* = 7.1 Hz, N-CH_2), 7.03 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.17 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.29–7.32 (m, 1H, Ar-H), 7.66 (d, 2H, *J* = 8.3 Hz, Ar-H), 7.89–7.95 (m, 1H, Ar-H), 8.05 (d, 1H, *J* = 7.9 Hz, Ar-H), 8.67 (brs, 2H, NH_2, D_2O exchangeable); MS *m/z* 479 ([M$^+$], 53%), 450 ([M$^+$–C_2H_5], 45%). Anal. Calcd for $C_{23}H_{18}ClN_5OS_2$ (479.9): C, 57.55; H, 3.78; N, 14.59. Found: C, 57.48; H, 3.85; N, 14.53.

8-Amino-2-acetyl-3-methyl-6-(4-chlorophenyl)-7-(benzothiazol-2-yl)-thiazolo[4,5-*a*]pyrido[2,3-*d*]pyrimidin-5-one (15). A solution of **7d** (5.36 g, 0.01 mol) in a 2:1 mixture of acetic anhydride and pyridine (30 mL) was stirred under reflux for 4 h. The reaction mixture was allowed to cool to room temperature and poured into cold water (100 mL). The precipitate was filtered off and crystallized as yellow crystals (benzene) in 73% yield, mp. 295–298 °C; IR (ν/cm^{-1}) 3400 (NH), 3067 (CH aryl), 2913 (CH alkyl), 1720, 1687 (2×CO), 1630 (C=N); ^{1}H NMR (DMSO-d_6, δ, ppm) 2.13 (s, 3H, CH_3), 2.87 (s, 3H, $COCH_3$), 7.02 (d, 2H, *J* = 8.3 Hz, Ar-H), 7.17 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.27 (t, 1H, *J* = 6.2 Hz, Ar-H), 7.56–7.62 (m, 3H, Ar-H), 7.85 (d, 1H, *J* = 7.7 Hz, Ar-H), 8.58 (brs, 2H, NH_2, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, δ, ppm) 20.1, 30.6 (2×CH_3), 109.6, 113.8, 114.6, 120.4, 122.3, 126.6, 128.8, 129.5, 130.6, 130.9, 136.2, 138.5, 142.0, 148.2, 158.1, 159.0, 159.4, 159.6, 160.3 (sp^2 carbons), 163.5, 187.4 (2×CO); MS *m/z* 517 ([M$^+$], 100%), 502 ([M$^+$–CH_3], 37%), 474 ([M$^+$–$COCH_3$], 56%). Anal. Calcd for $C_{25}H_{16}ClN_5O_2S_2$ (517.9): C, 57.96; H, 3.11; N, 13.52. Found: C, 58.01; H, 3.20; N, 13.49.

8-Amino-2-cinnamoyl-3-methyl-6-(4-chlorophenyl)-7-(benzothiazol-2-yl)-thiazolo[4,5-*a*]pyrido[2,3-*d*]pyrimidin-5-one (16). A mixture of **15** (5.18 g, 0.01 mol), 4-anisaldehyde (1.36 g, 0.01 mol) and a catalytic amount of piperidine was heated at 170–180 °C in a test tube for 4 h. The product was solidified by cooling and adding methanol (50 mL). The precipitate formed was collected by filtration, dried and crystallized as yellow powder (benzene) in 60% yield, mp. 260–263 °C; IR (ν/cm^{-1}) 3370 (NH), 3082 (CH aryl), 2935 (CH alkyl), 1703, 1687 (2×CO), 1640 (C=N); ^{1}H NMR (DMSO-d_6, δ, ppm) 3.39 (s, 3H, OCH_3), 5.32 and 5.52 (AB, 1H each, *J* = 8.1 Hz), 7.08 (d, 2H, *J* = 8.39 Hz, Ar-H), 7.14 (d, 1H, *J* = 7.5 Hz, Ar-H), 7.27 (t, 1H, *J* = 6.0 Hz, Ar-H), 7.34 (d, 2H, *J* = 8.41 Hz, Ar-H), 7.90 (t, 1H, *J* = 6.2 Hz, Ar-H), 7.85 (d, 1H, *J* = 7.9 Hz, Ar-H), 8.73 (brs, 2H, NH_2, D_2O exchangeable); MS *m/z* 636 ([M$^+$], 100%), 637 ([M$^+$+1], 32%). Anal. Calcd for $C_{33}H_{22}ClN_5O_3S_2$ (636.1): C, 62.30; H, 3.48; N, 11.01. Found: C, 62.27; H, 3.46; N, 10.96.

6. Biological Experimental Section

6. 1. Antibacterial Activity

The newly synthesized compounds were screened for their antibacterial activity against *Escherichia coli*

(ATTC-25922), *Staphylococcus aureus* (ATTC-25923), *Pseudomonas aeruginosa* (ATCC-27853) and *Klebsiella pneumaniae* (recultured) bacterial strains by serial plate dilution method.[19,20] Serial dilutions of the drug in Muller-Hinton broth were taken in tubes and their pH was adjusted to 5.0 using phosphate buffer. Standardized suspension of the tested bacterium was inoculated and incubated for 16–18 h at 37 °C. The minimum inhibitory concentration (MIC) was noted by observing the lowest concentration of the drug at which there was no visible growth. A number of antimicrobial discs are placed on the agar for the sole purpose of producing zones of inhibition in the bacterial lawn. Agar media were poured into each Peteri dish. Excess of suspension was decanted and placed in an incubator at 37 °C for 1 h drying the plates. Using an agar punch, wells were made on these seeded agar plates and minimum inhibitory concentrations of the test compounds in dimethylsulfoxide were added into each labeled well. A control was also prepared for the plates in the same way using the same solvent. The Petri dishes were prepared in triplicate and maintained at 37 °C for 3–4 days. Antibacterial activity was determined by measuring the diameter of inhibition zone. Activity of each compound was compared with Ciprofloxacin as standard.[21,22] Zone of inhibition was determined for the tested compounds and the results are summarized in Table 1.

6. 2. Antifungal Activity

Newly synthesized compounds were screened for their antifungal activity against *Aspergillus flavus* [NCIM No. 524], *Aspergillus fumigatus* [NCIM No. 902], *Peniciillium marneffei* (recultured) and *Trichophyton mentagrophytes* (recultured) in dimethylsulfoxide by serial plate dilution method.[23,24] Agar media were prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 mL) and adjusting the pH to 5.7. Normal saline was used to make a suspension of sporae of fungal strains for lawning. A loopful of particular fungal strain was transferred to 3 mL saline to get a suspension of corresponding species. Agar media of 20 mL were poured into each Petri dish. Excess of suspension was decanted and plates were dried by placing in an incubator at 37 °C for 1 h. Using an agar punch each labeled well was made on these seeded agar plates and minimum inhibitory concentration of the test compounds in dimethylsufoxide were added into each labeled well. A control was also prepared for the plates in the same way using the same solvent. The Petri dishes were prepared in triplicate and maintained at 37 °C for 3–4 days. Antifungal activity was determined by measuring the diameter of the inhibition zone. Activity of each compound was compared with Ciclopiroxolamine as standard. Zones of inhibition were determined for the tested compounds and the results are summarized in Table 2.

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Povzetek

Preučevana je bila priprava, reaktivnost in biološka aktivnost nove serije derivatov 7-amino-5-aril-6-(benzotiazol-2-il)-2-tioksopirido[2,3-*d*]pirimidin-4-ona. Raziskane so bile tudi pretvorbe aromatskih aldehidov, halogenidov in nekaterih hidrazonoil kloridov v ustrezne polikondenzirane heterociklične spojine, kot npr. 8-amino-7-(benzotiazol-2-il)-[1,3]tiazolo[4,5-*a*]pirido[2,3-*d*]pirimidin-3,5-dione, 3,9-diarilizoazolo[5´,4´:4,5]tiazolo-[3,2-*a*]pirido[2,3-*d*]pirimidin-10-one in 1,6-diaril ter 3-aril- ali 3-acetil- ali 3-etilkarboksilat- derivate 7-(benzotiazol-2-il)-pirido[2,3-*d*][1,2,4]triazolo[4,5-*a*]pirimidin-5-onov. Spojine so bile tudi *in vitro* testirane za morebitne antimikrobne učinke proti vrsti bakterij in gljiv.