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Utility of 6-Aryl-5-Cyano-2-Thiouracil Derivative as a Precursor for the Synthesis of Some New Pyrimidines

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Abstract Reactions of 6-aryl-5-cyano-2-thiouracil derivatives 1a,b with a variety of reagents leads to the synthesis of some new pyrimidines and condensed pyrimidines. The antibacterial activity was studied against examples of Gram-positive and Gram-negative bacteria.

Keywords Tetrazolopyrimidine, Diaminopyrimidine, Triazolopyrimidine, Thienopyrimidine, Antibacterial

1. Introduction

It is well known that pyrimidine derivatives are of great biological interest, especially as antimicrobial[1-4], Anti-HIV[5, 6], anti-inflammatory[7, 8] and antitumor agents[9-18]. Fused pyrimidines continue to attract considerable attention because of their great practical usefulness, primarily due to very wide spectrum of biological activities. This is evident in particular from publications of regular reviews on the chemistry of systems where the pyrimidine ring is fused to various heterocycles such as purines, pteridines, quinazolines, pyridopyrimidines, triazolo pyrimidines, pyrazolopyrimidines, pyrimidoazepines, furopyrimidines and pyrolopyrimidines. Many simple fused pyrimidines such as purines and pteridines are biologically active by themselves[19, 20], or are essential components of very important naturally occurring substances (i.e., nucleic acids). Some pteridine derivatives are also used as anti-leukemic drugs[21], or potassium-conserving diuretics[22]. In addition, several quinazoline alkaloids exhibit hypnotic[23, 24], bronchodilatory[25], and antimalarial[26, 27] activity. 2-Thiouracils and 6-aryl-2-thiouracils are well known for their antimicrobial, anticancer and antiviral activity[28-30]. The aim of this study was to synthesize some new pyrimidine derivatives based on 6-aryl-5-cyano-2-thiouracil derivative and to investigate their antibacterial activity.

2. Results and Discussion

2.1. Chemistry

In connection with our programme aiming to the synthesis and evaluate the biological activity of fused heterocycles [31-33], we have tried to prepare some condensed pyrimidines. Thioxopyrimidine 1 was condensed with chloroacetic acid and p-chlorobenzaldehyde in a mixture of acetic acid and acetic anhydride in the presence of fused sodium acetate to yield thiazolopyrimidine derivative 2[34]. The structure of compound 2 was confirmed by its analytical and spectral data. IR spectrum of 3 showed absorption bands at 2219, 1761 and 1694 cm^{-1} corresponding to C≡N and C=O groups, respectively. Its ^1H NMR spectrum showed signals at δ = 7.65-8.22 ppm corresponding to Ar-H and ethylenic proton.

The alkylation of methylthioxopyrimidine derivative 1b using chloroacetonitrile gave N-alkylated derivative 3. Its IR spectrum showed absorption bands at 2224 and 1686 cm^{-1} corresponding to C≡N and C=O groups, respectively. While its ^1H NMR spectrum showed two singlets at δ = 2.77 and 5.20 ppm corresponding to SCH_3 and CH_2, respectively.

Hydrazinolysis of 3 with hydrazine hydrate gave diaminopyrimidine derivative 4 via rearrangement[35]. IR spectrum of 4 showed absorption bands at 3428, 3330 cm^{-1} corresponding to NH and NH_2, in addition to two bands at 2209 and 1651 cm^{-1} corresponding to C≡N and C=O groups, respectively. Its ^1H NMR spectrum showed three singlets at δ = 4.15, 4.41 and 11.50 ppm for NH_2, CH_2 and NH, respectively.

The cyclocondensation of 4 with formic acid afforded triazolopyrimidine derivative 5[36]. The structure of 5 was elucidated by its IR and ^1H NMR spectra. IR spectrum showed absorption bands at 2221 and 1698 cm^{-1} corresponding to C≡N and C=O groups, respectively. Whereas ^1H NMR spectrum showed two singlets at δ = 5.14 and 8.8 ppm corresponding to CH_2 and N=CH, respectively. Treatment of compound 4 with nitrous acid at 0 °C gave tetrazolopyrimidine derivative 6. IR spectrum of compound 6 showed absorption bands at 2229 and 1707 cm^{-1}

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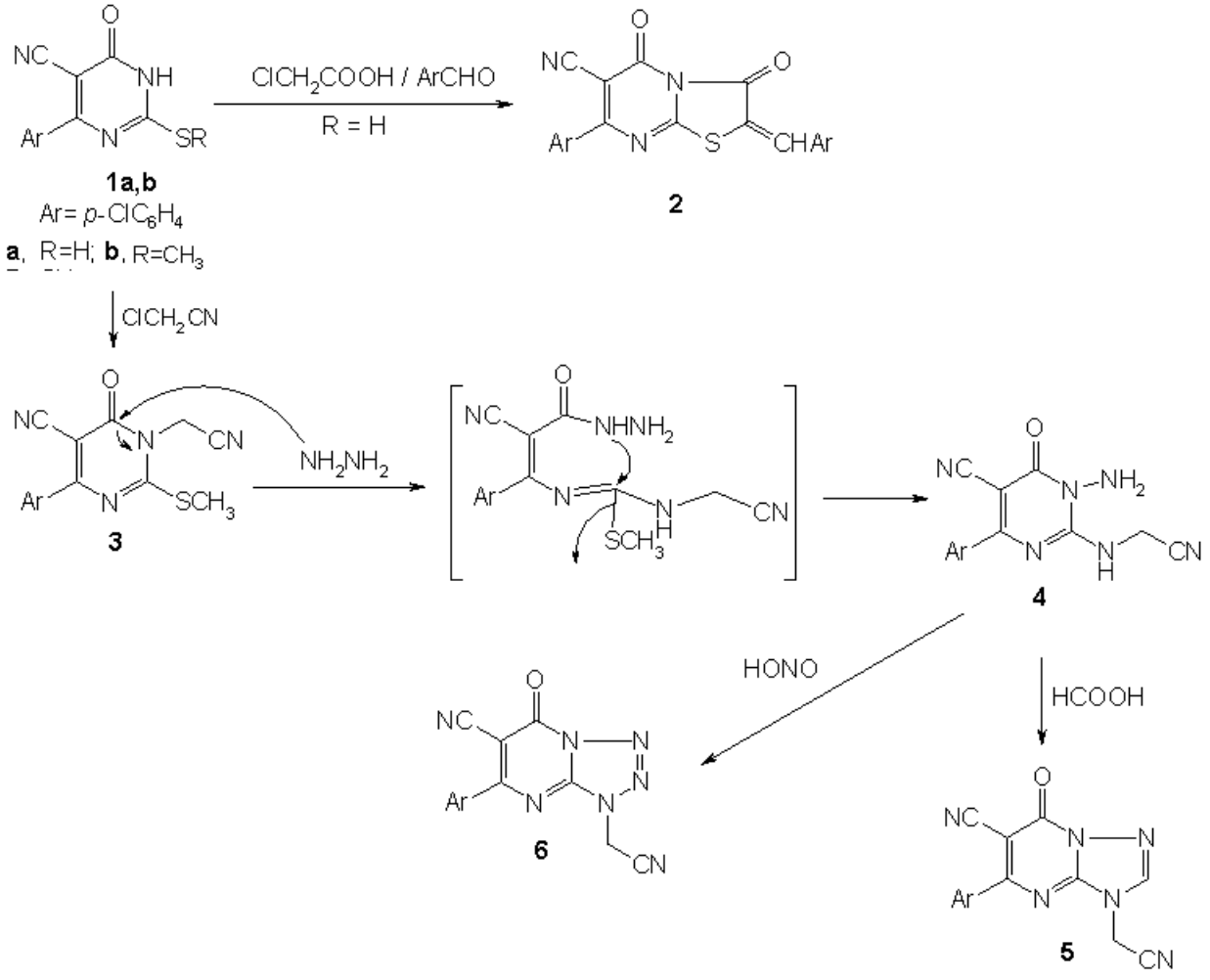
corresponding to C≡N and C=O, respectively. Its 1H NMR spectrum showed one singlet at δ = 5.33 ppm corresponding to CH_2 (Scheme 1).

Chlorination of pyrimidone 1b using phosphorous oxychloride produced chloropyrimidine derivative 7[37] in which Position 4 showed distinct activity and the chlorine atom could be replaced by aromatic amines namely, anthranilic acid, p-aminoacetophenone and/or o-phenylenediamine to give 4-aminoaryl pyrimidine derivatives 8a-c[38], respectively. The structures of compounds 8a-c were confirmed by their analytical and spectral data. IR spectrum of compound 8a showed absorption bands at 3438, 2210 and 1674 cm^{-1} corresponding to OH, C≡N and C=O groups, respectively. Its ^1H NMR spectrum showed three singlets at δ = 2.60, 11.89 and 13.92 ppm corresponding to SCH_3, NH and COOH, respectively. IR spectrum of compound 8b showed absorption bands at 2209 and 1676 cm^{-1} corresponding to C≡N and C=O groups, respectively. Its ^1H NMR spectrum showed three singlets at δ = 2.50, 2.56 and 10.11 ppm corresponding to SCH_3, $COCH_3$ and NH, respectively. IR spectrum of compound 8c showed absorption bands at 3422, 3308 cm^{-1} corresponding to NH and NH_2 groups, in addition to a band at 2209 cm^{-1} corresponding to C≡N group. Its Mass spectrum showed M^+ at 367 (40%).

Compound 8a underwent intramolecular cyclocondensation, when heated with acetic anhydride to give pyrimidoqinazoline derivative 9[39]. IR spectrum showed absorption bands at 2217 and 1693 cm^{-1} corresponding to C≡N and C=O groups, respectively. Its ^1H NMR spectrum showed one singlet at δ = 2.58 ppm corresponding to SCH_3. Treatment of com-pound 8c with nitrous acid at 0 ℃ yielded benzotriazolylpyrimidine derivative 10. IR spectrum of compound 10 showed an absorption band at 2215 cm^{-1} corresponding to C≡N group. Its ^1H NMR spectrum showed one singlet at δ = 2.77 ppm corresponding to SCH_3.

Reaction of 7 with hydrazine hydrate afforded dihydrazinylpyrimidine derivative 11[39]. The structure of 11 was elucidated by: (a) IR spectrum which showed absorption bands at 3400, 3303 cm^{-1} corresponding to NH and NH_2 groups, in addition to one absorption band at 2211 cm-1 corre-sponding to C≡N group. Its ^1H NMR spectrum showed two singlets at δ = 4.50 and 4.72 ppm corresponding to two NH_2, in addition to two singlets at δ = 8.85 and 11.87 ppm corresponding to two NH.

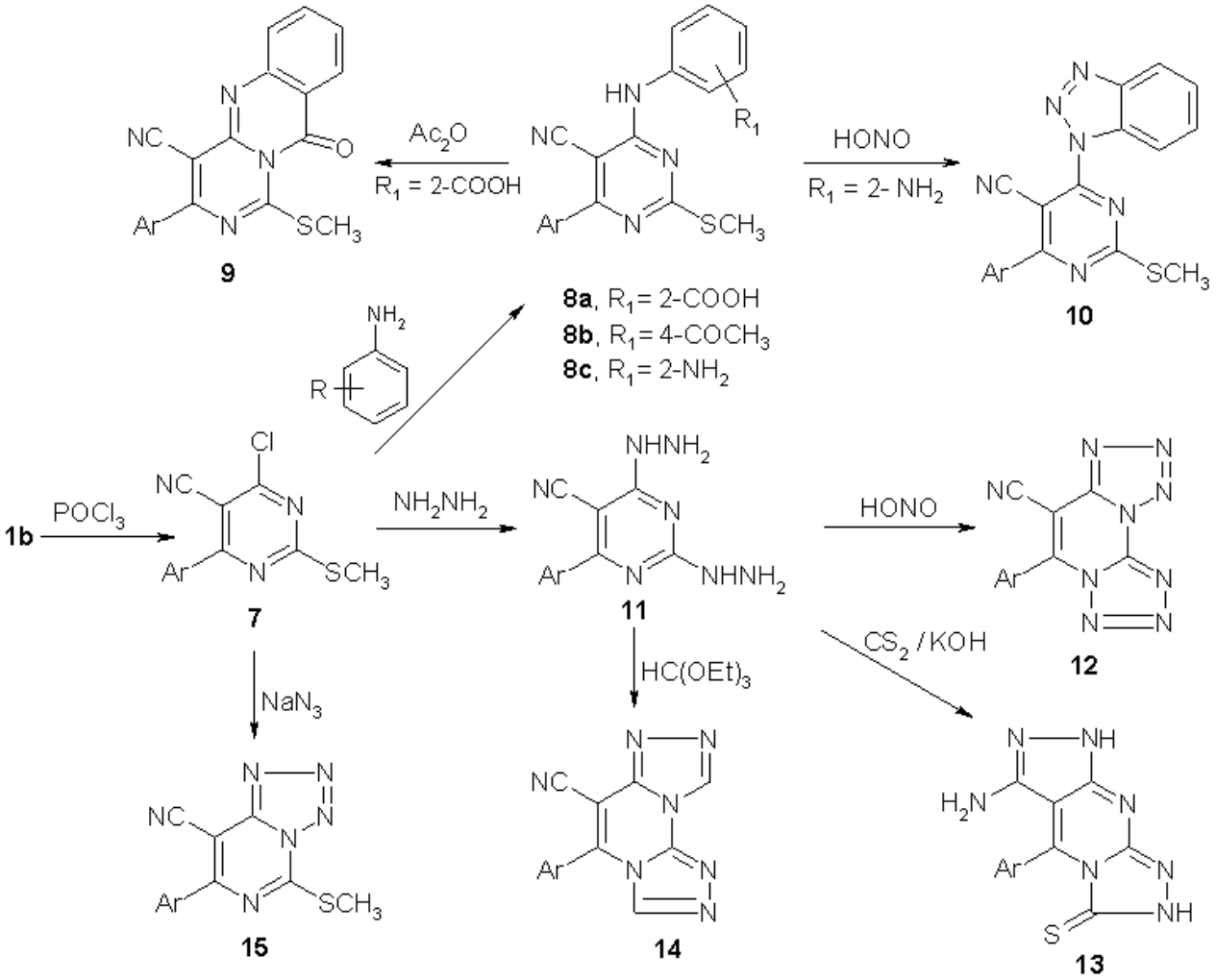


Scheme 1. Heterocyclization of thiouracil derivatives to azolopyrimidines 2,5 and 7

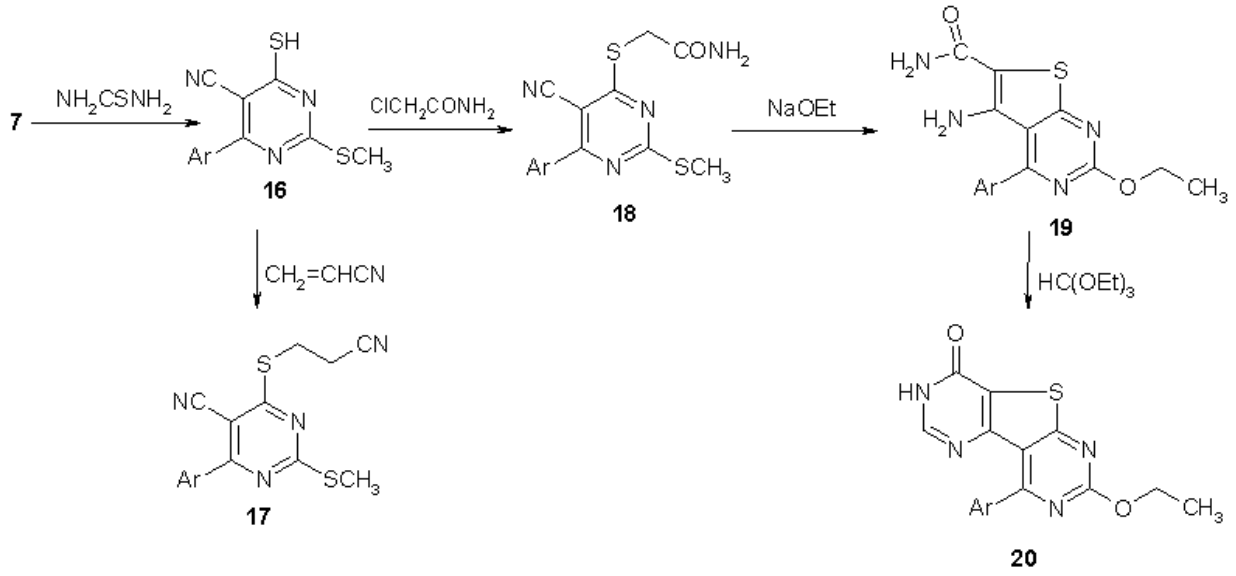
Compound 11 seemed to be of suitable located functionality for further heterocyclization affording triazolo, tetrazolo and thiazolo rings joined to pyrimidine nucleus. Thus, diazotization of compound 11 resulted in the formation of bis(tetrazolo)pyrimidine derivative 12[39]. The structure of 12 was elucidated by IR and ^{1}H NMR spectra. Its IR spectrum showed an absorption band at 2222 cm^{-1} corresponding to C≡N, whereas its ^{1}H NMR spectrum showed disappearance of the four signals of NH and NH_2 protons.

Heating compound 11 with carbon disulphide in ethanolic potassium hydroxide solution gave pyrazolotriazolopyrimidine derivative 13[40]. IR spectrum of compound 13 showed absorption bands at 3434, 3300 corresponding to NH and NH_2 groups, in addition to an absorption band at 1387 cm-1 corresponding to C=S group. Its ^{1}H NMR spectrum showed one singlet at δ = 6.02 ppm corresponding to NH_2, in addition to two singlets at δ = 12.27 and 13.96 ppm corresponding to two NH.

Reaction of compound 11 with triethyl orthoformate afforded bis(triazolo)pyrimidine derivative 14[41]. IR spectrum of compound 14 showed an absorption band at 2237 cm^{-1} corresponding to C≡N group. Whereas, its ^{1}H NMR showed two singlets at δ = 9.10 and 10.06 ppm corresponding to two N=CH. The reaction of chloropyrimidine derivative 7 with sodium azide afforded tetrazolopyrimidine derivative 15[42]. IR spectrum of compound 15 showed an absorption band at 2201 cm^{-1} corresponding to C≡N group. Its ^{1}H NMR showed one singlet at δ = 2.59 ppm corresponding to SCH_3 (Scheme 2).



Scheme 2. Heterocyclization of compound 7and 11



Scheme 3. Heterocyclization of compound 16

Refluxing 7 with thiourea in ethanol gave compound 16[37] which was reacted with acrylonitrile in presence of catalytic piperidine to give the addition product 17[43] . The structure of 17 was elucidated by its IR spectrum which showed an absorption band at 2211 cm^{-1} corresponding to C≡N group, and its ^{1}H NMR which showed one singlet at δ = 2.64 ppm corre-sponding to SCH_3, in addition to two triplets at δ = 3.04 and 3.61 ppm corresponding to two CH_2. Alkylation of 16 using chloroacetamide gave *S*-alkylated product 18[43]. The IR spectrum of compound 18 showed absorption bands at 2209 and 1660 cm^{-1} corresponding to C≡N and C=O groups, respectively. Its ^{1}H NMR showed three singlets at δ = 2.61, 4.06, 7.25 ppm corresponding to SCH_3, SCH_2 and $CONH_2$, respectively. Refluxing 18 in sodium ethoxide solution resulted in intramolecular cyclization affording thienopyrimidine derivative[43]. The structure of 19 was elucidated by its IR and 1H NMR spectra. IR spectrum of compound 19 showed absorption bands at 3313, 3275, 3219, 3178 cm^{-1} corresponding to NH2 and CONH2 groups, in addition to an absorption band at 1656 cm^{-1} corresponding to C=O group. Its ^{1}H NMR showed a triplet at δ = 1.35 ppm and a quartet at δ = 4.44 ppm corresponding to OCH_3CH_2, in addition to two singlets at δ = 6.16 and 7.20 ppm corresponding to NH_2 and $CONH_2$, respectively. Cyclization of 19 with triethyl orthoformate gave 20[44]. The IR spectrum of compound 20 showed absorption bands at 3440 and 1682 cm^{-1} corresponding to NH and C=O groups, respectively. Its ^{1}H NMR showed two singlets at δ = 8.16 and 12.90 ppm corresponding to CH-pyrimidine and NH, respectively (Scheme 3).

2.2. Antibacterial Activity

Compounds 3, 4, 6, 8a, 11, 12, 15, 17 and 18 were tested for in vitro an-timicrobial activity. Tetracycline was used as antibacterial agent ent standard. The zone of inhibition of bacterial growth around the disc was observed. The screening results given in Table 1 indicate that all the tested compounds have antibacterial activities against *Escherichia coli* and *Staphylococcus aureus*.

Table 1. In vitro antibacterial activities of some of the synthesized compounds

Sample		Inhibition zone diameter (mm)	
		Escherichia coli (G-)	Staphylococcus aureus (G+)
Control: DMSO		0.0	0.0
Standard	Tetracycline Antibacterial agent	30	25
3		9	10
4		12	13
6		10	12
8a		15	17
11		11	11
12		9	9
15		10	10
17		12	10
18		9	9

3. Experimental

All melting points are uncorrected. IR spectra (KBr) were run on a Unicam SP 1200G infrared spectrophotometer. ^{1}H NMR spectra (DMSO-d_6) were run on a Varian spectrometer (300 MHz) with a T.M.S. as internal standard. Elemental analyses and *in vitro* antimicrobial activities were carried out at Micro Analytical Center, Cairo University. Compounds **1a,b**, **7** and **16** were prepared by the procedures described in literature[37, 45].

7-(4-chlorophenyl)-2-[(4-chlorophenyl)methylidene]-3,5-dioxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carbonitrile (2). A mixture of **1a** (0.01 mol), chloroacetic acid (0.01 mol), *p*-chloro benzaldehyde (0.01 mol) and fused sodium acetate (2g) in glacial acetic acid (30 ml) and acetic anhydride (15 ml) was refluxed for 4h, cooled and The solid formed was filtered off, dried and recrystallized from acetic acid to give **2** as yellow crystals. m.p. > 300°C, Yield: 74% . IR (KBr) υ_{max}: 3086 (CH), 2219 (C≡N), 1761, 1694 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ: 7.65-8.22 (m, 9H, Ar-H + ethylenic proton) ppm. Anal. Calcd. for $C_{20}H_9Cl_2N_3O_2S$ (426.28): C, 56.35; H, 2.13; N, 9.86. Found: C, 56.28; H, 2.21; N, 9.77.

4-(4-Chlorophenyl)-1-(cyanomethyl)-2-(methylthio)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (3)

A mixture of **1b** (0.01 mol), chloroacetonitrile (0.01 mol) and K_2CO_3 (0.01 mol) in DMF (30 ml) was heated on a water bath for 5h, cooled and poured onto cold water. The solid formed was filtered off, washed with water then dried and recrystallized from EtOH to give **3** as brown crystals. m.p. 192-194 °C, Yield: 63%. IR (KBr) υ_{max}: 3085, 2951(CH), 2224 (C≡N), 1686 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ: 2.77 (s, 3H, CH_3), 5.20 (s, 2H, CH_2), 7.67-8.06 (m, 4H, Ar-H) ppm. Anal. Calcd. for $C_{14}H_9ClN_4OS$ (316.76): C, 53.08; H, 2.86; N, 17.69. Found: C, 53.13; H, 2.81; N, 17.62.

1-Amino-4-(4-chlorophenyl)-2-((cyanomethyl)amino)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (4)

A mixture of **3** (0.01 mol) and hydrazine hydrate (3 ml) in EtOH (50 ml) was refluxed for 4h, cooled and the solid formed was filtered off, dried and recrystallized from EtOH to give **4** as yellow crystals. m.p. > 300 °C, Yield: 73%. IR (KBr) υ_{max}: 3428, 3330 (NH, NH_2), 3070 (CH) and 2209 (C≡N), 1651 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ: 4.15 (s, br., 2H, NH_2), 4.41 (s, 2H, CH_2), 7.59-7.96 (m, 4H, Ar-H), 11.50 (s, br., 1H, NH) ppm. Anal. Calcd. for $C_{13}H_9ClN_6O$ (300.70): C, 51.92; H, 3.02; N, 27.95. Found: C, 52.01; H, 2.97; N, 27.89.

5-(4-chlorophenyl)-3-(cyanomethyl)-7-oxo-3,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carbonitrile (5)

A mixture of **4** (0.01 mol) and formic acid (20 ml) was refluxed for 6h. The formed precipitate after cooling was filtered off, dried and recrystallized from EtOH to give **5** as brown crystals. m.p. > 300 °C, Yield: 67% . IR (KBr) υ_{max}: 3104 (CH), 2221 (C≡N), 1698 (C=O), 1643 (C=N), 1601 (C=C) cm^{-1}. ^1H NMR (DMSO-d_6) δ: 5.14 (s, 2H, CH_2), 7.67-7.75 (m, 4H, Ar-H), 8.80 (N=CH) ppm. Anal. Calcd. for $C_{14}H_7ClN_6O$ (310.70): C, 54.12; H, 2.27; N, 27.05. Found: C, 54.17; H, 2.21; N, 26.98.

5-(4-chlorophenyl)-3-(cyanomethyl)-7-oxo-3,7-dihydrotetrazolo[1,5-a]pyrimidine-6-carbonitrile (6)

A stirred ice cold solution of compound **4** (0.01 mol) in acetic acid (20 ml) was treated drop wise with a cold solution of $NaNO_2$ (0.01 mol) in water (5 ml). The reaction mixture was further stirred for 30 min. then poured into cold water and the separated solid product was filtered off, washed with water, dried and recrystallized from EtOH to give **6** as brown crystals. m.p. 246-248 °C, Yield: 85%. IR (KBr) υ_{max}: 3086 (CH), 2229 (C≡N), 1707 (C=O), 1614 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6) δ: 5.33 (s, 2H, CH_2) 7.68-8.00 (m, 4H, Ar-H) ppm. Anal. Calcd. for $C_{13}H_6ClN_7O$ (311.69): C, 50.09; H, 1.94; N, 31.46. Found: C, 50.17; H, 1.91; N, 31.52.

2-{[6-(4-chlorophenyl)-5-cyano-2-(methylsulfanyl)pyrimidin-4-yl]amino}benzoic acid (8a)

A mixture of **7** (0.01 mol) and anthranilic acid (0.01 mol) in acetic acid (30 ml) was refluxed for 10h and the solid formed on hot was filtered off, dried and recrystallized from n-butanol to give **8a** as white crystals. m.p. 268-270 °C, Yield: 77%. IR (KBr) υ_{max}: 3438 (OH), 3115 (NH), 2929 (CH), 2210 (C≡N), 1674 (C=O), 1621(C=N) cm^{-1}. ^1H NMR (DMSO-d_6) δ: 2.60 (s, 3H, CH_3), 7.21-8.71(m, 8H, Ar-H), 11.89(s, 1H, NH), 13.92(s, 1H, COOH) ppm. Anal. Calcd. for $C_{19}H_{13}ClN_4O_2S$ (396.85): C, 57.50; H, 3.30; N, 14.12. Found: C, 57.56; H, 3.25; N, 14.17.

4-((4-acetylphenyl)amino)-6-(4-chlorophenyl)-2-(methylthio)pyrimidine-5-carbonitrile (8b) and **4-((2-aminophenyl)amino)-6-(4-chlorophenyl)-2-(methylthio)pyrimidine-5-carbonitrile (8c)**. A mixture of **7** (0.01mol),p-aminoacetophenone and/or o-phenylenediamine (0.01 mol) and K_2CO_3 (0.01 mol) in EtOH (50 ml) was refluxed for 3h and The solid formed on hot was filtered off, dried and recrystallized from the proper solvent to give **8b** and **8c**, respectively.

Compound **8b**

From *n*-butanol as yellow crystals. m.p. 256-258 °C, Yield: 65%. IR (KBr) υ_{max}: 3305 (NH), 2209 (C≡N), 1676 (C=O), 1604 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6) δ: 2.50 (s, 3H, SCH_3), 2.56 (s, 3H, $COCH_3$), 7.64-7.98 (m, 8H, Ar-H), 10.11 (s, br., 1H, NH) ppm. Anal. Calcd. for $C_{20}H_{15}ClN_4OS$ (394.88): C, 60.83; H, 3.83; N, 14.19. Found: C, 60.87; H, 3.79; N, 14.23.

Compound **8c**

From *n*-butanol as yellow crystals. m.p. 220-222 °C, Yield: 86%. IR (KBr) υ_{max}: 3422, 3308 (NH_2, NH), 2209 (C≡N), 1624 (C=N) cm^{-1}. MS: m/z = 367 (M^+), 352 (M^+-CH_3), 351 (M^+-NH_2), 332 (M^+-Cl), 320 (M^+-SCH_3). Anal. Calcd. for $C_{18}H_{14}ClN_5S$ (367.86): C, 58.77; H, 3.84; N, 19.04. Found: C, 58.82; H, 3.78; N, 18.96.

3-(4-chlorophenyl)-1-(methylthio)-10-oxo-10H-pyrimido[6,1-b]quinazoline-4-carbonitrile (9). A mixture of **8a** (0.01 mol) and acetic anhydride (30 ml) was refluxed for 6h then cooled and the precipitate formed was filtered off, dried and recrystallized from acetic acid to give **9** as yellow crystals. m.p. 262-264°C, Yield: 48%. IR (KBr) υ_{max}: 3073 (CH), 2217 (C≡N), 1693 (C=O), cm^{-1}. ^1H NMR (DMSO-d_6) δ: 2.58 (s, 3H, SCH_3), 7.53-8.22 (m, 8H, Ar-H) ppm. Anal. Calcd. for $C_{19}H_{11}ClN_4OS$ (378.83): C, 60.24; H, 2.93; N, 14.79. Found: C, 60.30; H, 2.89; N, 14.82

4-(1H-benzotriazol-1-yl)-6-(4-chlorophenyl)-2-(methylthio)pyrimidine-5-carbonitrile (10). A stirred cold solution of compound **8c** (0.01 mol) in conc. HCl (20 ml) was treated drop wise with a cold solution of $NaNO_2$ (0.01 mol) in water (5 ml). The reaction mixture was further stirred for 30 min. then poured into cold water and the separated solid product was filtered off, washed with water, dried and recrystallized

from n-butanol to give **10** as white crystals. m.p. 244-246 °C, Yield: 63%. IR (KBr) υ_{max}: 3079 (CH), 2215 (C≡N) cm^{-1}. ^1H NMR (DMSO-d_6) δ: 2.77 (s, 3H, SCH_3), 7.67-8.42 (m, 8H, Ar-H) ppm. Anal. Calcd. for $C_{18}H_{11}ClN_6S$ (378.84): C, 57.07; H, 2.93; N, 22.18. Found: C, 57.12; H, 2.89; N, 22.15.

4-(4-chlorophenyl)-2,6-bis(hydrazino)pyrimidine-5-carbonitrile (11). A mixture of **7** (0.01 mol) and hydrazine hydrate (5 ml) in ethanol (50 ml) was refluxed for 6h. The formed precipitate after cooling was filtered off, dried and recrystallized from *n*-butanol to give **11** as yellow crystals. m.p. 240-242 °C, Yield: 86%. IR (KBr) υ_{max}: 3400, 3303, (NH, NH_2), 3099, 3054 (CH), 2211 (C≡N) cm^{-1}. ^1H NMR (DMSO-d_6) δ: 50 (s, br., 2H, NH_2), 4.72 (s, br., 2H, NH_2), 7.55-7.85 (m, 4H, Ar-H), 8.85 (s, br., 1H, NH), 11.87 (s, br., 1H, NH) ppm. Anal. Calcd. for $C_{11}H_{10}ClN_7$ (275.70): C, 47.92; H, 3.66; N, 35.56. Found: C, 47.88; H, 3.71; N, 35.62.

5-(4-chlorophenyl)bistetrazolo[1,5-a:1',5'-c]pyrimidine-6-carbonitrile (12). A stirred cold solution of compound **11** (0.01 mol) in acetic acid (50 ml) was treated drop wise with a cold solution of $NaNO_2$ (0.01 mol) in water (5 ml). The reaction mixture was further stirred for 30 min. then poured into cold water and the separated solid product was filtered off, washed with water, dried and recrystallized from EtOH to give **12** as white crystals. m.p. 144-146 °C, Yield: 73%. IR (KBr) υ_{max}: 3084 (CH), 2222 (C≡N) cm^{-1}. ^1H NMR (DMSO-d_6) δ: 7.69-8.01 (m, 4H, Ar-H) ppm. Anal. Calcd. for $C_{11}H_4ClN_9$ (297.66): C, 44.39; H, 1.35; N, 42.35. Found: C, 44.42; H, 1.31; N, 42.39.

6-amino-5-(4-chlorophenyl)-2,8-dihydro-3H-pyrazolo[3,4-d][1,2,4]triazolo[4,3-a]pyrimidine-3-thione (13).

A mixture of **11** (0.01 mol), CS_2 (5 ml) and KOH (0.02 mol) in ethanol (75 ml) was refluxed for 6h. After removal of the solvent under vacuum, water was added and the alkaline solution was neutralized with diluted HCl. The formed precipitate was filtered off, washed with water then dried and recrystallized from DMF/EtOH to give **13** as yellow crystals. m.p. > 300 °C, Yield: 62%. IR (KBr) υ_{max}: 3434, 3300 (NH, NH_2), 1387 (C=S) cm^{-1}. ^1H NMR (DMSO-d_6) δ: 6.02 (s, br., 2H, NH_2), 7.61-7.95 (m, 4H, Ar-H), 12.27 (s, br., 1H, NH), 13.96 (s, br., 1H, NH) ppm. Anal. Calcd. for $C_{12}H_8ClN_7S$ (317.76): C, 45.36; H, 2.54; N, 30.86. Found: C, 45.42; H, 2.49; N, 30.91.

5-(4-chlorophenyl)bis[1,2,4]triazolo[4,3-a:4',3'-c]pyrimidine-6-carbonitrile (14). A mixture of **11** (0.01 mol) and triethyl orthoformate (10 ml) in acetic acid (30 ml) was refluxed for 4h. The precipitate formed during heating was filtered off, dried and recrystallized from DMF to give **14** as orange crystals. m.p. > 300 °C, Yield: 54%. IR (KBr) υ_{max}: 3076 (CH), 2237(C≡N), 1630(C=C), 1589 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6) δ: 7.80-7.87 (m, 4H, Ar-H), 9.10 (s, 1H, N=CH), 10.06 (s, 1H, N=CH) ppm. Anal. Calcd. for $C_{13}H_6ClN_7$ (295.69): C, 52.81; H, 2.05; N, 33.16. Found: C, 52.78; H, 2.10; N, 33.12.

7-(4-chlorophenyl)-5-(methylthio)tetrazolo[1,5-c]pyrimidine-8-carbonitrile (15). A mixture of **7** (0.01 mol) and sodium azide (0.01 mol) in acetic acid (30 ml) was refluxed for 4h, cooled and the formed precipitate was filtered off, dried and recrystallized from EtOH to give **15** as white crystals. m.p. 294-296 °C, Yield: 73%. IR (KBr) υ_{max}: 2921 (CH), 2201(C≡N) cm^{-1}. ^1H NMR (DMSO-d_6) δ: 2.59 (s, 3H, SCH_3), 7.62-7.99 (m, 4H, Ar-H) ppm. Anal. Calcd. for $C_{12}H_7ClN_6S$ (302.74): C, 47.61; H, 2.33; N, 27.76; Found: C, 47.58; H, 2.37; N, 27.81.

4-(4-chlorophenyl)-6-[(2-cyanoethyl)thio]-2-(methylthio)pyrimidine-5-carbonitrile (17). A mixture of **16** (0.01 mol), acrylonitrile (0.01 mol) and few drops of piperidine in n-butanol (30 ml) was refluxed for 3h, cooled and the formed precipitate was filtered off, dried and recrystallized from n-butanol to give **17** as white crystals. m.p. 152-154 °C, Yield: 78%. IR (KBr) υ_{max}: 3076, 2993 (CH), 2211(C≡N) cm^{-1}. ^1H NMR (DMSO-d_6) δ: 2.64 (s, 3H, SCH_3), 3.04 (t, 2H, CH_2), 3.61 (t, 2H, CH_2), 7.65-7.96 (m, 4H, Ar-H) ppm. Anal. Calcd. for $C_{15}H_{11}ClN_4S_2$ (346.86): C, 51.94; H, 3.20; N, 16.15. Found: C, 51.89; H, 3.23; N, 16.18.

2-{[6-(4-chlorophenyl)-5-cyano-2-(methylthio)pyrimidin-4-yl]thio}acetamide (18). A mixture of **16** (0.01 mol), cyanoacetamide (0.01 mol) and anhydrous sodium acetate (0.01 mol) in absolute ethanol (50 ml) was refluxed for 3h, cooled and the formed precipitate was filtered off, dried and recrystallized from n-butanol to give **18** as white crystals. m.p. 220-222 °C, Yield: 77%. IR (KBr) υ_{max}: 3370, 3188 (NH_2), 2978 (CH), 2209 (C≡N), 1660 (C=O), 1597 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6) δ: 2.61 (s, 3H, SCH_3), 4.06 (s, 2H, SCH_2), 7.25 (s, br., 2H, $CONH_2$), 7.65-7.95 (m, 4H, Ar-H) ppm. Anal. Calcd. for $C_{14}H_{11}ClN_4OS_2$ (350.84): C, 47.93; H, 3.16; N, 15.97. Found: C, 47.89; H, 3.21; N, 16.01.

5-amino-4-(4-chlorophenyl)-2-ethoxythieno[2,3-d]pyrimidine-6-carboxamide (19). A mixture of **18** (0.01 mol) and 50 ml ethoxide solution (prepared by dissolving 0.01 mol of Na in 50 ml absolute ethanol) was refluxed for 1h, cooled and poured onto cold water. The solid formed was filtered off, washed with water then dried and recrystallized from EtOH to give **19** as yellow crystals. m.p. 210-212 °C, Yield: 48%. IR (KBr) υ_{max}: 3313, 3275, 3219, 3178 (NH_2, $CONH_2$), 2972 (CH), 1656 (C=O), 1593 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6) δ: 1.35 (t, 3H, CH_3), 4.44 (q, 2H, CH_2), 6.16 (s, br., 2H, NH_2), 7.20 (s, br., 2H, NH_2), 7.60-7.68 (m, 4H, Ar-H) ppm. Anal. Calcd. for $C_{15}H_{13}ClN_4O_2S$ (348.81): C, 51.65; H, 3.76; N, 16.06. Found: C, 51.69; H, 3.71; N, 16.02.

9-(4-chlorophenyl)-7-ethoxypyrimido[4',5':4,5]thieno[2,3-d]pyrimidin-4(3H)-one (20). A mixture of **19** (0.01 mol) and triethyl orthoformate (10 ml) in acetic anhydride (20 ml) was refluxed for 4h then cooled and poured into cold water. The precipitate formed was filtered off, dried and recrystallized from n-butanol to give **20** as yellow crystals. m.p. > 300 °C, Yield: 54%. IR (KBr) υ_{max}: 3440 (NH), 3061, 2981 (CH), 1682 (C=O), 1583(C=N) cm^{-1}. ^1H NMR (DMSO-d_6) δ: 1.39 (t, 3H, CH_3), 4.50 (q, 2H, CH_2), 7.53-7.88 (m, 4H, Ar-H), 8.16 (s, 1H, CH-pyrimidine), 12.90 (s, br., 1H, NH) ppm. Anal. Calcd. for $C_{16}H_{11}ClN_4O_2S$ (358.81): C, 53.56; H, 3.09; N, 15.61. Found: C, 53.61; H, 3.05; N, 15.64.

4. Conclusions

Using 6-aryl-5-cyano-2-thiouracil derivative as a precursor, several novel pyrimidines were synthesized. The antibacterial screening for some of the synthesized compounds indicated that all the tested compounds have antibacterial activities on the tested microorganisms.

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