Synthesis, Antitumor and Antimicrobial Testing of Some New Thiopyrimidine Analogues

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The synthesis of some new 4-chloro-pyrimidine-5-carbonitriles (3b–d), 4-substituted-amino-pyrimidine-5-carbonitriles (4a–g), trioxo and dioxo-thiazolo[3,2-*a*]pyrimidine-6-carbonitriles (5a–c and 6a–h) have been described. The obtained compounds were evaluated for their *in-vitro* antitumor activity. A single dose (10 μM) of the test compounds was used in the National Cancer Institute (NCI) 60 cell lines panel assay. Compounds 3c and 4f showed high inhibitory activity against leukemia, whereas, compounds 3b and 4d, g displayed moderate activity. On the other hand, all compounds were screened for their *in-vitro* antibacterial and antifungal activities. Compounds 3d and 4b exhibited significant antibacterial activity against *Staphylococcus aureus*. Compound 4e showed two folds inhibitory activity against *Entrobacter aerogener* compared with the reference drug Tobramycin.

Key words thiopyrimidine derivative; synthesis; antitumor; antimicrobial activity

Thiouracil, 5-Flurouracil[1] (**A**) and other pyrimidine compounds are important synthons in anticancer, antibacterial and antifungal chemotherapy.[2–5] *S*-Alkylation (**B**) and *N*-alkylation (**C**) products of thiouracil analogues have been recently reported as novel antibacterial, and cytotoxic agents.[6,7] Thiazolopyrimidines (**D**), the bioisostere analogues of the anticancer purines such as Thioguanine[8,9] (Lanvis®) (**E**), are potentially bioactive molecules reported to display significant anticancer and antimicrobial activities[10–13] (Fig. 1).

The development of potent and effective novel antineoplastic drugs is one of the most intensely persuaded goals of contemporary medicinal chemistry. In view of the biological significance of thiouracils and in continuation of our previous efforts in the synthesis of new thiouracils and uracil-related heterocycles,[7] we would like to report herein the synthesis of new thioxo-chloro-pyrimidines (**3b–d**), substituted-aminopyrimidines (**4a–g**) and thiazolopyrimidines (**5a–c**, **6a–h**) and their antitumor, antimicrobial testing.

Results and Discussion

Chemistry The 6-chloro-pyrimidine derivatives **3a–d** is used as a key precursor in the present study. They were synthesized using the reported method for compound **3a**.[14] (Chart 1). Thus compounds **1a–d** was treated with alkyl halides to give the corresponding *S*-alkylated derivatives **2a–d** followed by phosphoryl chloride treatment to afford **3a–d**. The structure of the newly prepared compounds **3b–d** was confirmed by elemental analyses and spectral data (IR, ^{1}H-NMR and MS). The IR spectra of these compounds showed the disappearance of both NH and C=O bands. ^{1}H-NMR spectra of compounds **3b–d** showed the absence of NH signal. Moreover mass spectrum of compound **3c** showed molecular ion peaks at *m/z* 307.05 (M^+) (33.17%) and 309.05 (M+2) (13.09%) in ratio 3 : 1 indicating the presence of chlorine atom.

2-Alkylthio-6-aryl-4-substituted-aminopyrimidine-5-carbonitriles (**4a–g**) were prepared through direct reaction of 2-alkylthio-4-aryl-6-chloropyrimidine-5-carbonitrile with various amines, in the presence of potassium carbonate in boiling

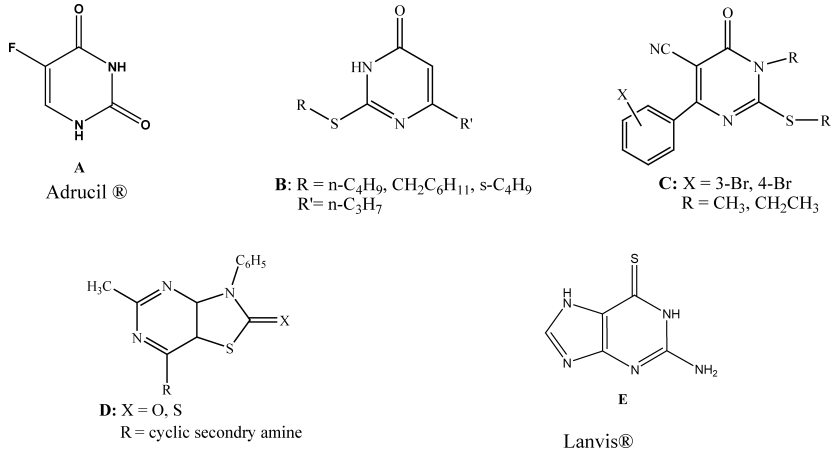

Fig. 1. Some Literature Cited Antitumor Thiopyrimidine Analogues

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dry benzene.[15] Supporting evidence for structures of newly prepared compounds **4a–g** was provided by microanalyses and spectral data (IR, ^{1}H-NMR and MS). The ^{1}H-NMR spectra of compounds **4a–c** showed signals of piperidyl protons around δ 1.39, 1.70 and 3.87 ppm. While ^{1}H-NMR spectrum of **4d** pointed to triplet signal at δ 3.27 and δ 3.72 ppm of morphinyl protons.

On the other hand, in Chart 2 the thiazolopyrimidinetriones **5a–c** were prepared in 50–55% yield, by treatment of **1a–c** with oxalyl chloride under dry condition. Compounds **5a–c** may exist in one of two forms **F** and **G**. Based on the literature reports[16,17] the chemical shift of the pyrimidinone carbonyl is markedly affected by the nature of the adjacent nitrogen. To distinguish between the two forms **F** and **G**, ^{13}C-NMR of compounds **5b** were recorded. The data showed signals for the carbonyl carbon resonance at δ=175.99 ppm. This chemical shift suggests that N(3) near to C=O is sp^2-hybridized (pyridine type as in compound **I**) appears at 170–175 ppm and different from the sp^3-hybridized nitrogen (pyrrole type), the carbonyl carbon C-4, which appears at 160–164 ppm (compound **H**) (Fig. 2).[16,17] Based on the above finding, we conclude that the isolated products are found in each case in one form namely, **F** rather than **G**.

IR, ^{1}H-NMR, and mass spectra were consistent with the proposed structures.

Moreover, reaction of 6-aryl-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitriles (**1a–h**) with chloroacetyl chloride in dry benzene[18] afforded thiazolopyrimidinediones **6a–h**. Confirmatory evidence for structures of the novel synthesized compounds **6a–h** was given by elemental analyses and spectral data (IR, ^{1}H-NMR and MS). The IR spectra showed the disappearance of NH band and appearance of two absorption bands at 1740, 1650 cm^{-1} of two carbonyl group. ^{1}H-NMR showed that CH_2 of thiazolidinone appeared as two singlet peaks around at δ 3.47 and 4.45 ppm. Based on literature survey[19,20] and three dimension data (Fig. 3) of compounds **6a–h**, it revealed that one proton of (CH_2) was incorporated within the shielding cone of the aromatic ring in the 6-position so appeared in ranging 3.47–3.78 ppm, while the other proton was affected by deshielding effect of the adjacent carbonyl group so appeared in ranging 4.00–4.45 ppm. This supports the hypothesis that the cyclization may occur at N(1) rather than N(3).

Biological Evaluation The antitumor screening of novel synthesized compounds was carried-out at the National Cancer Institute (NCI), Bethesda, MD, U.S.A. However, the antimicrobial testing was carried-out at Department of Microbiology, Faculty of Pharmacy, Misr University for Science and Technology, Cairo, Egypt.

Preliminary *in-Vitro* Antitumor Screening The synthesized compounds (**3b**, **c**, **4a–g**, **5a–c**, and **6a–h**) were subjected to the NCI's disease-oriented human cell lines screening assay to be evaluated for their *in-vitro* antitumor activity. A single dose (10 μm) of the tested compounds was used in the full NCI 60 cell lines panel assay which includes nine tumor subpanels namely; leukemia, non-small cell lung, colon, CNS, melanoma, ovarian, renal, prostate, and breast cancer cells.[21–24] The data reported as mean graph of the percent growth of the treated cells, and presented as percentage growth inhibition (GI%). The obtained results of the tested thioxopyrimidinones and their analogues are shown in Table 1.

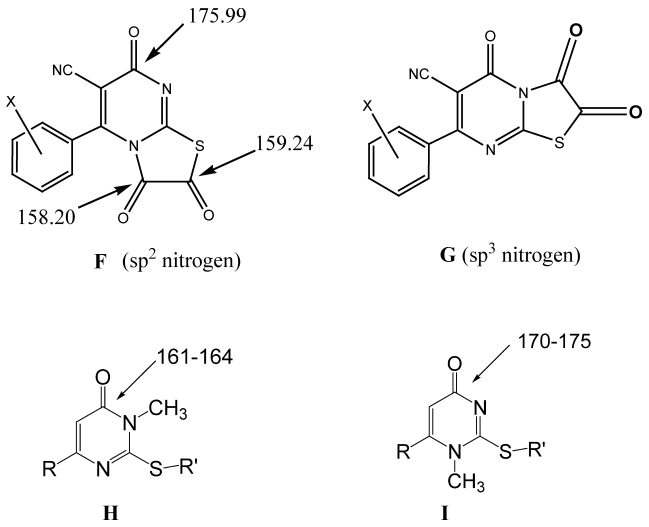

Fig. 2. ^{13}C-NMR Chemical Shift of Reported Thiouracil

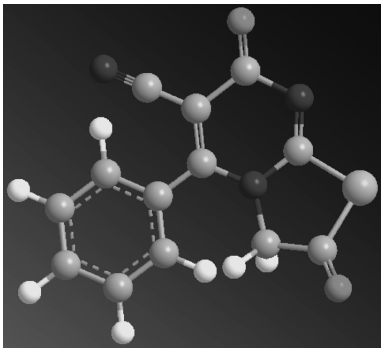

Fig. 3. Three Dimension of Compounds **6a–h**

Antimicrobial Activity The testing of the antimicrobial activity of all novel derivatives was carried out at Department of Microbiology, Faculty of Pharmacy, Misr University for Science and Technology using the disc diffusion technique according to Wiart.[25] The tested strains included *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Enterobacter aerogener* ATCC 23048, *Klebsiella* ATCC 23495, *Salmonella*, and *Candida albicans*. The diameters of the measured zones showing complete inhibition were recorded to the nearest millimeter. The mean of the inhibition zone was tabulated in Table 2.

Determination of the Minimum Inhibitory Concentration (MIC) MIC values of the synthesized compounds (**3b–d**, **4b**, **f**, **5a**, **b** and **6d**, **f**, **g**) were determined with *S. aureus* ATCC 25923 using Tobramycin as reference drug according to broth dilution method.[26] The results were represented in Table 3 and Fig. 4.

Results of *in-Vitro* Antitumor Screening The obtained results of tested compounds showed that compounds **3b**, **c** and **4f** possessed an excellent activity against some leukemia cell line with GI values >70%. However, other compounds exhibited moderate to weak activity against most of the cell lines.

Regarding the activity toward individual cell lines: the 4-chlorothiopyrimidine derivative **3b** showed remarkable activity against CCRF-CEM, K-562 and MOLT-4 leukemia cell lines with GI values 93, 84 & 93, respectively. In addition, it exerted moderate activity against HCT-116 colon cancer and

Table 1. Percentage Growth Inhibition (GI%) of *in Vitro* Sensitive Tumor Cell Lines at 10 μM Concentration of Tested Compounds

Compds. No.	Cell line		GI%	Compds. No.	Cell line		GI%
3b	Leukemia	CCRF-CEM	**93**	**4e**	Ovarian cancer	OVCAR- 5	13
		K-562	**84**	**4f**	Leukemia	CCRF-CEM	**93**
		MOLT-4	**93**			RPMI-8226	29
		RPMI-8226	22		Non-small cell lung cancer	NCI-H522	15
	Non-small cell lung cancer	NCI-H522	14		Colon cancer	HCT-116	**34**
	Colon cancer	HCT-116	**38**			HCT-115	12
		HCT-15	**13**			SW-620	30
		SW-620	28		CNS cancer	U251	12
	Melanoma	LOX IMVI	30		Melanoma	LOX IMVI	**38**
	Renal cancer	UO-31	14			M14	12
3c	Leukemia	CCRF-CEM	**36**		Renal cancer	UO-31	14
		K-562	17	**4g**	Leukemia	CCRF-CEM	22
		MOLT-4	**25**			K-562	22
		SR	**72**			MOLT-4	27
4a	Leukemia	CCRF-CEM	13			RPMI-8226	21
		MOLT-4	10		Non-small cell lung cancer	NCI-H226	23
	Non-small cell lung cancer	NCI-H522	18			NCI-322 m	26
	Melanoma	UACC-62	16		CNS cancer	SF-295	18
4c	Melanoma	UACC-62	17			SF-539	18
	Ovarian cancer	OVAR-5	11			U251	19
	Renal cancer	786-0	17		Prostate cancer	PC-3	20
		A-498	17		Breast cancer	MCF7	21
4d	Leukemia	CCRF-CEM	19			T-47D	19
		MOLT-4	28			MDA-MB-231/ATCC	15
		RPMI-8226	18	**5a**	Non-small cell lung cancer	Hop-92	22
		SR	19	**5b**	Renal cancer	UO-31	22
	Non-small cell lung cancer	EKVX	12	**5c**	Renal cancer	A498	30
		Hop-92	21		Leukemia	RPMI-8226	23
		NCI-H522	24		Melanoma	UACC-62	20
	Colon cancer	HCT-15	16	**6a**	Non-small cell lung cancer	Hop-92	12
		HT29	18		Prostate cancer	PC-3	16
	CNS cancer	SF-295	18	**6b**	Leukemia	SR	15
		SNB-75	18	**6d**	Renal cancer	UO-31	27
	Melanoma	SK-MEL-5	15	**6g**	Non-small cell lung cancer	EKVX	11
		UACC-62	23			Hop-92	14
	Ovarian cancer	OVCAR- 4	16				
	Renal cancer	786-0	20				
		A498	29				
		RXF 393	17				
		UO-31	**34**				
	Prostate cancer	PC-3	12				
	Breast cancer	MCF-7	17				
		MDA-MB-231/ATCC	13				
		T-47D	21				
		MDA-MB-468	11				

LOX-IMVI melanoma with GI values 38 & 30, respectively. Meanwhile, compound **3c** registered distinctive potential selectivity against SR leukemia panel and moderate activity against CCRF-CEM leukemia cell line with GI values 72 & 36%, respectively. The 4-substituted aminothiopyrimidines **4a**–**g** recorded low activity against most of the tumor cell lines.

As an exception of compound **4f** which proved to be having an excellent selective activity to CCRF-CEM with GI value 93% and moderate activity against HCT-116, SW-620 colon cancer and LOX-IMVI melanoma with GI values 34, 30 & 38%, respectively. Meanwhile, compound **4d** showed moderate

Table 2. The Preliminary Antimicrobial and Antifungal Screening Test for the Prepared Compounds Using Tobramycin and Fluconazole as References, DMSO as Control

Compds. No.	*Staph. aureus*	*Salmoenella*	*E. coli*	*Klebsiella*	*Enterobacter*	*Candida albicans*
3b	18 mm	—	—	—	—	—
3c	19 mm	—	—	—	—	—
3d	22 mm	—	—	—	—	—
4a	—	—	—	—	—	—
4b	22 mm	—	—	—	—	—
4c	—	—	—	—	—	—
4d	—	—	—	—	—	—
4e	—	—	14 mm	—	**34** mm	7 mm
4f	15 mm	—	—	—	—	—
4g	20 mm	—	—	—	—	—
5a	13 mm	—	—	—	—	—
5b	9 mm	—	—	—	—	—
5c	—	—	—	—	—	—
6a	—	—	—	—	—	—
6b	—	—	—	—	—	9 mm
6c	—	—	—	—	—	—
6d	7 mm	—	—	—	—	—
6e	—	—	—	—	—	—
6f	7 mm	—	—	—	—	7 mm
6g	10 mm	—	—	—	—	—
6h	—	—	—	—	—	7 mm
Tobramycin	29 mm	—	23 mm	—	20 mm	—
Fluconazole						28
Sulphadiazine	21	—	16	—	—	—
Sulphamethoxazole	20	—	18	—	—	—
DMSO	—	—	—	—	—	—

Table 3. Minumum Inhibitory Concentration Values of the Compound with *S. aureus*

Compds. No.	**3c**	**3d**	**4b**	**4f**	**5a**	**5b**	**6d**	Sulphadiazine	Sulphamethoxazole	Tobramycin
MIC value (μg/mL)	16	8	8	32	64	64	128	8	16	1

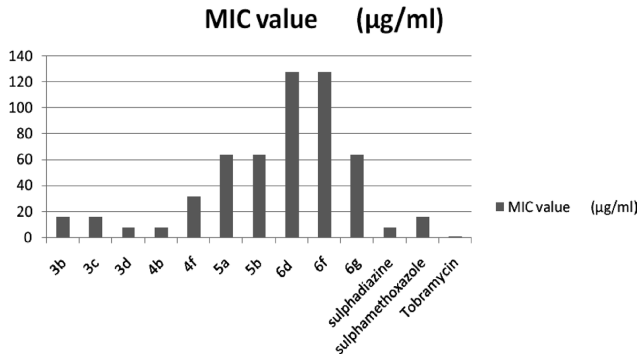

Fig. 4. Minumum Inhibitory Concentration Values of Compounds **3b**–**d**, **4f**, **5a**,**b** & **6d**,**f**,**g**

activity against UO-31 renal cancer with GI value 34%.

Considering the fused thiazolopyrimidinones **5a**–**c** and **6a**–**h** demonstrated mild activity against the tested cell lines. The highest activity within these classes of compounds was observed with compound 5c against A498 renal cancer with GI value 30%.

Results of Antimicrobial Activity Compounds **3b**, **c** and **4f** showed moderate activity against *S. aureus* with inhibition zone 18, 19 and 15 mm compared with 29 mm of the reference Tobramycin drug. On the other hand, compounds **3d** and **4b**, **g** registered promising activity with an inhibition zone 22, 22 and 20 mm, respectively. While compound **4e** proved to be most active member against *E. aerogener* ATCC 23048 with an inhibition zone doubling the reference drug. Compounds **4e** and **6b**, **f**, **h** displayed poor activity against *C. albicans*.

Structure Activity Correlation 4-Chlorothiopyrimidine compounds **3c** and **3b** have higher activity than that of **4a** and **4b** respectively, and this could be assigned to the presence of the active chlorine atom which favors the potency than that piperidine moiety.[27)]

Compound **4a** (4-flouroisopropyl derivative) showed selective activity toward CCRF-CEM, K-562 leukemia cell lines and H522 non-small cell lung cancer compared to 4-bromo isopropyl analogy **4c**. This could be assigned to the higher electronegativity of the fluorine atom at the aromatic ring manipulated the selectivity of the compound against specific cell lines.[28,29)] In addition that, compound **4c** (4-bromoisopropyl piperidino derivative) showed moderate selective activity against UACC-62 melanoma, OVACAR-5 ovarian cancer and 786-0, A 498 renal cancer compared to compound **4b** (3-bromoethylpiperidino derivative). This is may be referred to the combined factors of the difference in the position of

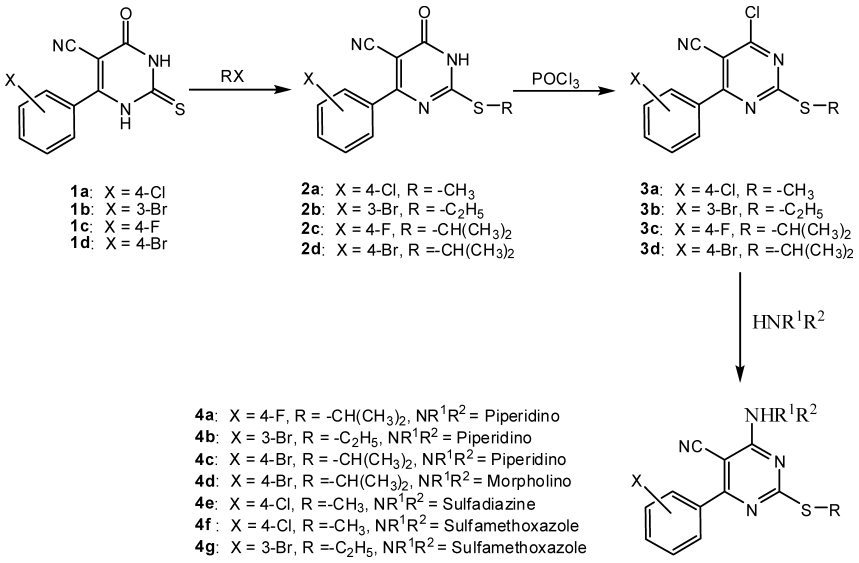

Chart 1

the halogen atom and the lipophilic character of isopropyl thioether substituent which enhances the potency than that of the methyl or ethyl derivatives. The hydrophobicity–activity relationship of alkyl moieties was found in various bioactive compounds.[30–33)]

Compound **4d** (morpholino derivative) displayed good activity against all leukemia panels, EKVX, HOP-92, NCI-H522 non small cell lung cancer, HCT-15, HT29 colon cancer, SF-295, SNB-75 CNS cancer, SK-MEL-5 melanoma, OVCAR- 4 ovarian cancer, RXF 393, UO-31 renal cancer, PC-3 prostate cancer and MCF-7, MDA-MB-231/ATCC, T-47D, MDA-MB-468 breast cancer compared to piperidino analogy **4c**. It seems that morpholino derivative is more preferred than piperidino congener.[34–37)] Compound **4f** displayed an excellent inhibition activity against CCRF-CEM, RPMI-8226 leukemia cell lines, HCT-116, SW-620 colon cancer, LOX-IMVI melanoma and good inhibitory activity against NCI-H522 non-small cell lung cancer, HCT-15 colon cancer, U251 CNS cancer, M14 melanoma and UO-31 renal cancer compared to **4e** (sulphadiazine derivative). It is presumably due to sulphamethoxazole moiety which enhances the antitumor activity.[38)] On the other hand, compound **4e** exerted selective activity against OVCAR-5 ovarian cancer compared to compound **4f**. Compound **4g** (sulphamethoxazole derivative) registered decent inhibition activity against most of leukemia cell lines, in addition to NCI-H226, NCI-322 m non-small cell lung cancer, SF-295, Sf-539, U251 CNS cancer, PC-3 prostate cancer and MCF7, T-47D, MDA-MB-231/ATCC breast cancer compared to piperidino analogy **4b** due to the presence of sulphamethoxazole moiety.[38)] Moreover, in chart 2 Compound **5a** showed superior inhibition activity against Hop-62 non-small lung cell line more than **6a** congener. Compound **5b** displayed selective activity against HOP-62 non-small cell lung cancer and UO-31 renal cancer compared to thiazolidindione derivative **6b**. In addition, compound **5c** recorded an inhibitory activity toward CCRF-CEM, RPMI-8226 leukemia cell lines, H226 non-small cell lung cancer, SNB-75 CNS cancer, LOXIMVI, UACC-257, UACC-62 melanoma, A498, CAKI-1 renal cancer and MCF7 breast cancer compared to thiazolidindione analogy **6c**. Generally, the fusion of thiazolone ring with the pyrimidinone nucleus afforded the hybrid series **5a**–**c** and **6a**–**h**, with diminished the potency of antitumor activity.

On the other hand, all chloro derivatives **3b**–**d** possessed an inhibitory activity against *S. aureus*. It may be that the effect of chlorine atom at position-4 favors the antibacterial activity. Meanwhile, compounds **4b** and **4g** showed decent antibacterial activity, this may be attributed to the presence of piperidino and sulphamethoxazole moieties which enhances the antimicrobial activity.[39,40)] Additionally, compounds **3d**, **4b** and **4g** exhibited comparable activity to the sulphadiazine and sulphamethoxazole reference drugs against *S. aureus*, while compound **4e** displayed equipotent activity toward *E. coli* in comparison with sulphadiazine standard drug. Moreover, compound **4e** showed an excellent inhibition activity against *E. aerogener* ATCC 23048, this is due to the presence of sulphadiazine moiety.[41)]

Conclusion

According to the results of bioactivities, it is noted that compounds **3b**, **c** and **4f** showed promising antitumor activity against leukemic cell panel than the other pyrimidine derivatives. Compounds **4d**, **f**, **g** possessed moderate to weak anticancer activity against most of the cancer cell line used. On the other hand, compounds **3d** and **4b** exhibited significant inhibitory activity against *S. aureus* than the other tested compounds with MIC 8 μg/mL. Compound **4e** was the most active derivative against *E. aerogener* ATCC 23048 with an inhibition zone 34 mm about two folds more than that of the reference Tobramycin antibiotic. Compounds **4e** and **6b**, **f**, **h** displayed antifungal activity against *C. albicans*. In conclusion, the study leads to the identification of novel cytotoxic compounds **3b,c** and **4f** as potential anticancer activity against certain leukemia panels. Whereas, compounds **3d** and **4b** exhibited significant antibacterial activity against *S. aureus*. Compound **4e** showed twice an inhibitory activity in comparison with that of the reference compound. These findings demonstrated a new potential for 4-substitutedpyrimidin derivatives which could be useful templates for further derivatives to obtain more potent antitumor agent(s).

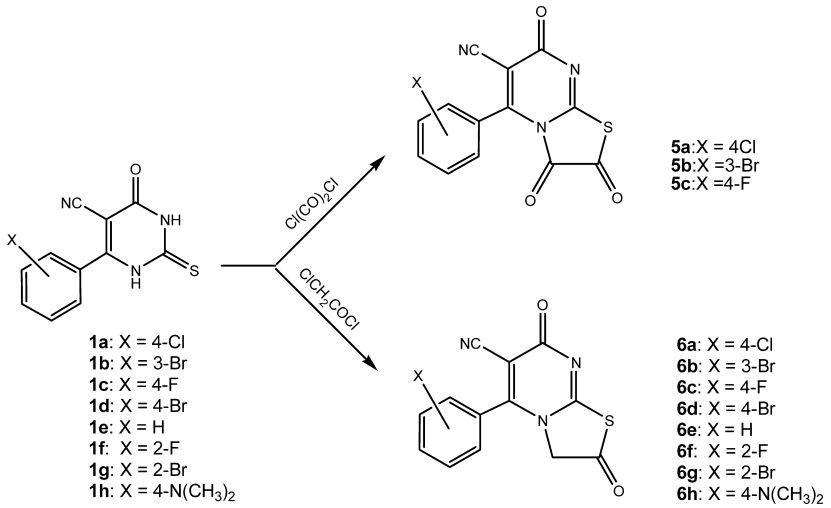

Chart 2

Experimental

General Melting points were determined on Stuart apparatus and the values given are uncorrected. IR spectra were recorded on Shimadzu IR 435 spectrophotometer and values were represented in cm[1]. ^{1}H- and ^{13}C-NMR were carried out on Varian Gemini 300 MHz spectrophotometer at The Microanalytical Center, Cairo University, Cairo, Egypt, using TMS as an internal standard and chemical shifts were recorded in ppm on δ scale. The electron impact (EI) mass spectra were recorded on Hewlett Packard 5988 spectrometer at The Microanalytical Center, Cairo University, Cairo, Egypt, Analytical thin layer chromatoghraphy (TLC) on silica gel olates containing UV indicator was employed routinely to follow the course of reactions and to check the purity of products. Elemental microanalyses were performed at The Microanalytical Center, Cairo University, Cairo, Egypt, and were within ±0.4%.

Compounds **1a**–**h**, **2a**–**d** and 4-chloro-6-(4-chlorophenyl)-2-(methylthio)pyrimidine-5-carbonitrile (**3a**) were prepared following reported procedures.[7,14]

2-Alkylthio-6-aryl-4-chloropyrimidine-5-carbonitrile (3a–d) A suspension of **2a**–**d** (0.0017 mol) and phosphorus oxychloride (6 mL) was heated under reflux for 5 h. Excess phosphorus oxychloride was evaporated under reduced pressure to half its volume. The reaction mixture was poured onto ice cold water (15 mL) with continuous stirring. The formed precipitate was filtered, dried and crystallized from acetone.

4-Chloro-6-(4-fluorophenyl)-2-(isopropylthio)pyrimidine-5-carbonitrile (**3b**): White micro crystals; yield 79%; mp: 86-87°C; IR (KBr, cm^{-1}): 2981, 2877 (C–H aliphatic), 2225 (CN); ^{1}H-NMR (DMSO-d_6): δ 1.39 (d, 6H, J=6.9 Hz, C$\underline{H}_3$–CH–C$\underline{H}_3$), 4.03 (sept, 1H, J=6.9 Hz CH$_3$–C$\underline{H}$–CH$_3$), 7.38–7.44 (dd, 2H, J=8.7, C$_2$,C$_6$ Ar$\underline{H}$), 7.99–8.04 (dd, 2H, J=8.7 Hz, J=5.4 Hz, C$_3$,C$_5$ Ar$\underline{H}$); ^{13}C-NMR (DMSO): δ 22.06 (2C), 36.69, 101.04, 114.65, 115.78, 116.08, 130.65, 131.68, 131.75, 162.45, 165.97, 167.04, 174.43; MS (EI) *m/z*: 307.05 (M$^+$, 33.17%), 309.05 (M+2, 13.09%), 274.05 (100%); *Anal*. Calcd for $C_{14}H_{11}ClFN_3S$ (307.77): C, 54.63; H, 3.60; N, 13.65; S, 10.42. Found: C, 54.78; H, 3.63; N, 13.53; S, 10.21.

6-(3-Bromophenyl)-4-chloro-2-(ethylthio)pyrimidine-5-carbonitrile (**3c**): White micro crystals; yield 69%; mp: 180–182°C; IR (KBr, cm^{-1}): 2966, (C–H aliphatic), 2229 (CN); ^{1}H-NMR (DMSO-d_6): δ 1.33 (t, 3H, J=7.2 Hz S–CH$_2$–C$\underline{H}_3$), 3.23 (q, 2H, J=7.2 Hz S–C$\underline{H}_2$–CH$_3$), 7.51–8.06 (m, 4H, Ar$\underline{H}$); ^{13}C-NMR (DMSO): δ 13.83, 25.56, 100.98, 114.60, 121.90, 127.99, 130.94, 131.42, 134.75, 136.01, 162.10, 166.20, 175.00; MS (EI) *m/z*: 353.00 (M$^+$, 72.61%), 355.00 (M+2, 100%), 357.00 (M+4, 27.52%); *Anal*. Calcd for $C_{13}H_9BrClN_3S$ (354.65): C, 44.03; H, 2.56; N, 11.85. Found: C, 43.86; H, 2.28; N, 11.92.

6-(4-Bromophenyl)-4-chloro-2-(isopropylthio)pyrimidine-5-carbonitrile (**3d**): Yellowish white micro crystals; yield 84%; mp: 88–90°C; IR (KBr, cm^{-1}): 2970, 2866 (C–H aliphatic), 2220 (CN); ^{1}H-NMR (DMSO-d_6): δ 1.41 (d, 6H, J=6.9 Hz C$\underline{H}_3$–CH–C$\underline{H}_3$), 3.96 (sept, 1H, J=6.9 Hz CH$_3$–C$\underline{H}$–CH$_3$), 7.63–7.91(m, 4H, Ar$\underline{H}$); ^{13}C-NMR (DMSO): δ 22.13, 22.42, 36.81, 101.26, 114.60, 126.29, 130.52, 130.59, 131.64, 131.91, 133.39, 162.38, 167.25, 174.62; *Anal*. Calcd for $C_{14}H_{11}BrClN_3S$ (368.68): C, 45.42; H, 3.01; N, 11.40; S, 8.70. Found: C, 45.57; H, 2.98;N, 11.29; S, 8.3.

2-Alkylthio-6-aryl-4-substitutedaminopyrimidine-5-carbonitrile (4a–g) A suspension of **3a**–**d** (0.0015 mol), anhydrous potassium carbonate (0.28 g, 0.002 mol) and substituted amine (0.0015 mol) in dry benzene (10 mL) was heated under reflux for 8 h. The reaction mixture was filtered while hot. The formed precipitate was filtered, washed with water, dried and crystallized from methanol.

6-(4-Fluorophenyl)-2-(isopropylthio)-4-(piperidin-1-yl)pyrimidine-5-carbonitrile (**4a**): White micro crystals; yield 62%; mp: 108–110°C; IR (KBr, cm^{-1}): 2927,2862 (C–H aliphatic), 2202 (CN); ^{1}H-NMR (DMSO-d_6): δ 1.37 (d, 6H, C$\underline{H}_3$–CH–C$\underline{H}_3$), 1.39 (br s, 2H, C$\underline{H}_2$ piperidine), 1.66 (br, 4H, 2CH$_2$ piperidine), 3.80 (sept, 1H, CH$_3$– C$\underline{H}$–CH$_3$), 3.87 (br, 4H, 2C$\underline{H}_2$ piperidine), 7.34–7.39 (dd, 2H, J=8.7 Hz, C$_2$,C$_6$ Ar$\underline{H}$), 7.88–7.92 (dd, 2H, J=8.7, C$_3$,C$_5$ Ar$\underline{H}$); ^{13}C-NMR (DMSO): δ 22.45(2C), 23.66, 25.05(2C), 35.66, 47.83(2C), 82.92, 115.16, 115.46, 117.92, 131.60, 131.72, 132.68, 161.21, 165.36, 168.76, 172.43; MS (EI) *m/z*: 356.15 (M$^+$, 74.12%), 313.10 (100%); *Anal*. Calcd for $C_{19}H_{21}FN_4S$ (356.46): C, 64.02; H, 5.94; N, 15.72. Found: C, 63.83; H, 5.96; N, 15.60.

6-(3-Bromophenyl)-2-(ethylthio)-4-(piperidin-1-yl)pyrimidine-5-carbonitrile (**4b**): Buff micro crystals; yield 65%; mp: 220–221°C; IR (KBr, cm^{-1}): 2922,2852 (C–H aliphatic), 2200 (CN); ^{1}H-NMR (DMSO-d_6): δ1.42 (t, 3H, J=7.2 Hz, S–CH$_2$–C$\underline{H}_3$), 1.58 (br s, 2H, C$\underline{H}_2$ piperidine), 1.75 (br, 4H, 2CH$_2$

piperidine), 3.15 (q, 2H, J=7.2 Hz, S–C$\underline{H}_2$–CH_3), 3.93 (br, 4H, 2C$\underline{H}_2$ piperidine), 7.32–7.99 (m, 4H, Ar$\underline{H}$); ^{13}C-NMR (DMSO): δ 14.38, 23.65, 24.86, 25.52 (2C), 47.81(2C), 83.39, 117.71, 121.42, 128.16, 130.47, 131.58, 133.62, 138.47, 160.93, 168.40, 172.52; *Anal*. Calcd for $C_{18}H_{19}BrN_4S$ (403.34): C, 53.60; H, 4.75; N, 13.89; S, 7.95. Found: C, 53.57; H, 4.77; N, 13.89; S, 7.88.

6-(4-Bromophenyl)-2-(isopropylthio)-4-(piperidin-1-yl)pyrimidine-5-carbonitrile (**4c**): Faint yellow micro crystals; yield 59%; mp: 128–130°C; IR (KBr, cm^{-1}): 2931, 2850 (C–H aliphatic), 2206 (CN); ^{1}H-NMR (DMSO-d_6): δ 1.37 (d, 6H, J=6.9 Hz, C$\underline{H}_3$–CH–C$\underline{H}_3$), 1.40 (s, 2H, C$\underline{H}_2$ piperidine), 1.66 (br, 4H, 2CH_2 piperidine), 3.77 (sept, 1H, J=6.9 Hz, CH_3–C$\underline{H}$–CH_3), 3.87 (br, 4H, 2C$\underline{H}_2$ piperidine), 7.70–7.81 (m, 4H, Ar$\underline{H}$); ^{13}C-NMR (DMSO-d_6) δ 22.50(2C), 23.62, 25.48(2C), 35.71, 47.83(2C), 83.05, 117.73, 124.73, 131.10(2C), 131.33(2C), 135.48, 161.22, 169.90, 172.55; MS (EI) m/z: 416.15 (M$^+$, 60.38%), 418.15 (M+2, 64.18), 375.10 (100%); *Anal*. Calcd for $C_{19}H_{21}BrN_4S$ (417.37): C, 54.68; H, 5.07; N, 13.42. Found: C, 54.71; H, 5.40; N, 13.67.

6-(4-Bromophenyl)-2-(isopropylthio)-4-morpholinopyrimidine-5-carbonitrile (**4d**): White micro crystals; yield 55%; mp: 140–141°C; IR (KBr, cm^{-1}): 2966, 2866 (C–H aliphatic), 2202 (CN); ^{1}H-NMR (DMSO-d_6): δ 1.38 (d, 6H, C$\underline{H}_3$–CH–C$\underline{H}_3$), 3.27 (t, 4H, 2C$\underline{H}_2$–N morpholine), 3.73 (sep, 1H, CH_3–C$\underline{H}$–CH_3), 3.88 (t, 4H, 2C$\underline{H}_2$–O morpholine), 7.45–7.77(m, 4H, Ar$\underline{H}$)); ^{13}C-NMR (DMSO-d_6) δ 22.41 (2C), 35.72, 46.96 (2C), 65.75 (2C), 83.53, 117.63, 124.89, 130.88, 131.06, 131.18, 131.38, 135.19, 161.44, 168.79, 172.56; MS (EI) m/z: 418.00 (M+, 41.79%), 420.00 (M+2, 40.83%), 385.00 (100%); *Anal*. Calcd for $C_{18}H_{19}BrN_4OS$ (419.34): C, 51.56; H, 4.57; N, 13.36. Found: C, 51.29; H, 4.32; N, 13.20.

4-((6-(4-Chlorophenyl)-5-cyano-2-(methylthio)pyrimidin-4-yl)amino)-*N*-(pyrimidin-2-yl)benzenesulfonamide (**4e**): Brownish yellow micro crystals; yield 62%; mp: 158–159°C; IR (KBr, cm^{-1}): 3425, 3356 (2NH), 2931, 2870 (C–H aliphatic), 2222 (CN); ^{1}H-NMR (DMSO-d_6): δ 2.61 (s, 3H, S–C$\underline{H}_3$), 7.65–8.47 (m, 11H, Ar$\underline{H}$), 8.41, 8.50 (2s, 2H, N$\underline{H}$ exchangeable by D_2O); *Anal*. Calcd for $C_{22}H_{16}ClN_7O_2S_2$ (509.99): C, 51.81; H, 3.16; N, 19.23. Found: C, 51.94; H, 3.76; N, 19.33.

4-((6-(4-Chlorophenyl)-5-cyano-2-(methylthio)pyrimidin-4-yl)amino)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (**4f**): Buff micro crystals; yield 57%; mp: 126-128°C; IR (KBr, cm^{-1}): 3400, 3300 (2NH), 2900, 2850 (C–H aliphatic), 2220 (CN); ^{1}H-NMR (DMSO-d_6): δ 2.30 (s, 3H, CH_3 of oxazole), 2.64 (s, 3H, S–C$\underline{H}_3$), 6.16 (s, 1H, CH of oxazole), 7.63–8.03 (m, 8H, Ar$\underline{H}$), 10.23, 11.41 (2s, 2H, N$\underline{H}$ exchangeable by D_2O); *Anal*. Calcd for $C_{22}H_{17}ClN_6O_3S_2$ (512.99): C, 51.51; H, 3.34; N, 16.38. Found: C, 51.90; H, 3.39; N, 16.72.

4-((6-(3-Bromophenyl)-5-cyano-2-(ethylthio)pyrimidin-4-yl)amino)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (**4g**): Buff micro crystals; yield 60%; mp: 234–235°C; IR (KBr, cm^{-1}): 3429, 3302 (2NH), 2966, 2927 (C–H aliphatic), 2214 (CN); ^{1}H-NMR (DMSO-d_6): δ 1.20 (t, 3H, J=7.2 Hz S–CH_2–C$\underline{H}_3$), 2.15 (s, 3H, CH_3 of oxazole), 3.00 (q, 2H, J=7.2 Hz S–C$\underline{H}_2$–CH_3), 5.87 (s, 1H, CH of oxazole), 7.54–7.99 (m, 4H, Ar$\underline{H}$), 7.83, 10.20 (2s, 2H, N$\underline{H}$ exchangeable by D_2O); ^{13}C-NMR (DMSO): δ 13.31, 14.21, 29.25, 82.10, 101.34, 114.71, 115.68, 120.52, 121.12, 122.85, 128.67, 128.95, 130.50, 130.89, 133.62, 133.98, 136.61, 137.29, 160.67, 162.35, 165.77, 166.88, 175.26; *Anal*. Calcd for $C_{23}H_{19}BrN_6O_3S_2$ (571.47): C, 48.34; H, 3.35; N, 14.71; S, 11.22. Found: C, 48.01; H, 3.15; N, 14.40; S, 10.96.

5-Aryl-2,3,7-trioxo-2,3-dihydro-7*H*-thiazolo[3,2-*a*]-pyrimidine-6-carbonitrile (5a–c) A mixture of **1c**, **1d** or **1g** (0.001 mol), anhydrous potassium carbonate (0.28 g, 0.002 mol) and oxalyl chloride (0.13 mL, 0.0015 mol) in dry benzene (15 mL) was heated under reflux for 8 h. The reaction mixture was filtered while hot and the filtrate was left to cool. The formed precipitate was filtered, washed with water, dried and crystallized from methanol.

5-(4-Chlorophenyl)-2,3,7-trioxo-2,3-dihydro-7*H*-thiazolo-[3,2-*a*]pyrimidine-6-carbonitrile (**5a**): Dark yellow micro crystals; yield 53%; mp: 244–246°C; IR (KBr, cm^{-1}): 2229 (CN) 1720 (N–C=O), 1702 (S–C=O), 1680 (CH–CO–N); ^{1}H-NMR (DMSO-d_6): δ 7.63–7.73 (m, 4H, ArH); MS (EI) m/z: 316.0 (M-1, 0.42%), 138.00 (100%); *Anal*. Calcd for $C_{13}H_4ClN_3O_3S$ (317.71): C, 49.15; H, 1.27; N, 13.23. Found: C, 49.40; H, 1.33; N, 13.41.

5-(3-Bromophenyl)-2,3,7-trioxo-2,3-dihydro-7*H*-thiazolo-[3,2-*a*]pyrimidine-6-carbonitrile (**5b**): Yellow micro crystals; yield 58%; mp: 170–172°C; IR (KBr, cm^{-1}): 2229 (CN) 1720 (N–C=O), 1701 (S–C=O), 1674 (CH–CO–N); ^{1}H-NMR (DMSO-d_6): δ 7.50–7.89 (m, 4H, ArH); ^{13}C-NMR (DMSO-d_6) δ 91.19, 114.31, 120.70, 121.28, 127.79, 130.55, 131.26, 131.33, 134.50, 134.65, 158.20, 159.24, 175.99; MS (EI) m/z: 316 (M-1, 0.42%), 138 (100%); *Anal*. Calcd for $C_{13}H_4BrN_3O_3S$ (362.16): C, 43.11; H, 1.11; N, 11.60; Found: C, 43.00; H, 1.19; N, 11.78.

5-(4-Fluorophenyl)-2,3,7-trioxo-2,3-dihydro-7*H*-thiazolo-[3,2-a]pyrimidine-6-carbonitrile (**5c**): Brownish red micro crystals; yield 51%; mp: 122–123°C; IR (KBr, cm^{-1}): 2225 (CN) 1720 (N–C=O), 1700 (S–C=O), 1689 (CH–CO–N); ^{1}H-NMR (DMSO-d_6): δ 7.03–7.87 (m, 4H, ArH); MS (EI) m/z: 301.10 (M$^+$, 3.06%), 77.00 (100%); *Anal*. Calcd for $C_{13}H_4FN_3O_3S$ (301.25): C, 51.83; H, 1.34; N, 13.95. Found: C, 51.91; H, 1.70; N, 13.58.

5-Aryl-2,7-dioxo-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile (6a–h) A mixture of **1a**–**h** (0.001 mol), anhydrous potassium carbonate (0.28 g, 0.002 mol) and chloroacetyl chloride (0.12 mL, 0.0015 mol) in dry benzene (15 mL) was heated under reflux for 10 h. The reaction mixture was filtered while hot. The formed precipitate was filtered, washed with water, dried and crystallized from methanol.

5-(4-Chlorophenyl)-2,7-dioxo-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile (**6a**): Dark yellow micro crystals; yield 90%; mp: >360°C; IR (KBr, cm^{-1}): 2927 (C–H aliphatic), 2214 (CN), 1735 (S–C=O), 1685 (N–C=O); ^{1}H-NMR (DMSO-d_6) δ 3.52, 4.35 (2s, 2H, N–C$\underline{H}_2$–CO), 7.39–7.90 (m, 4H, Ar$\underline{H}$); ^{13}C-NMR (DMSO): δ 57.09, 91.10, 114.63, 128.72, 128.76, 130.72, 130.83, 133.85, 137.17, 158.46, 165.92, 169.29, 176.21; MS (EI) m/z: 302.20 (M-1, 6.02%), 303.20 (M$^+$, 7.33%), 304.20 (M+1, 17.90%), 305.20 (M+2, 8.29%), 203.15 (100%); *Anal*. Calcd for $C_{13}H_6ClN_3O_2S$ (303.72): C, 51.41; H, 1.99; N, 13.83. Found: C, 51.52; H, 2.11; N, 13.94.

5-(3-Bromophenyl)-2,7-dioxo-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile (**6b**): Dark yellow micro crystals; yield 64%; mp: 220–221°C; IR (KBr, cm^{-1}): 2927, 2854 (C–H aliphatic), 2218 (CN), 1700 (S–C=O), 1681 (N–C=O); ^{1}H-NMR (DMSO-d_6) δ 3.78, 3.90 (2s, 2H, N–C$\underline{H}_2$–CO), 7.40–7.91 (m, 4H, Ar$\underline{H}$); *Anal*. Calcd for $C_{13}H_6BrN_3O_2S$ (348.17): C, 44.85; H, 1.74; N, 12.07. Found: C, 45.16; H, 1.82; N, 12.19.

5-(4-Fluorophenyl)-2,7-dioxo-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile (**6c**): Dark buff micro crystals; yield 69%; mp: 270–271°C; IR (KBr, cm^{-1}): 2930 (C–H aliphatic), 2220 (CN), 1700–(S–C=O), 1685 (N–C=O); ^{1}H-NMR (DMSO-d_6): δ 3.76, 4.40 (2s, 2H, N–C$\underline{H}_2$–CO), 7.24–7.28 (m, 1H, C_2Ar$\underline{H}$), 7.29–7.38 (m, 1H, C_6 Ar$\underline{H}$), 7.81–7.84 (m, 1H, C_3 Ar$\underline{H}$), 7.85–7.96 (m, 1H, C_5 Ar$\underline{H}$); MS (EI) *m*/*z*: 287.00 (M^+, 50.7%), 75.00 (100%); *Anal*. Calcd for $C_{13}H_6FN_3O_2S$ (287.27): C, 54.35; H, 2.11; N, 14.63; Found: C, 54.72; H, 2.29; N, 14.88.

5-(4-Bromophenyl)-2,7-dioxo-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile (**6d**): Brownish yellow micro crystals; yield 62%; mp: 210–212°C; IR (KBr, cm^{-1}): 2935, 2846 (C–H aliphatic), 2225 (CN), 1735-(S–C=O), 1654 (N–C=O); ^{1}H-NMR (DMSO-d_6): δ 3.72, 4.07 (2s., 2H, N–C$\underline{H}_2$–CO), 7.62–7.88 (m, 4H, Ar$\underline{H}$); *Anal*. Calcd for $C_{13}H_6BrN_3O_2S$ (348.17): C, 44.85; H, 1.74; N, 12.07. Found: C, 44.85; H, 1.72; N, 12.07.

2,7-Dioxo-5-phenyl-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile (**6e**): Faint brown micro crystals; yield 60%; mp: 258–260°C; IR (KBr, cm^{-1}): 2927 (C–H aliphatic), 2229 (CN), 1700 (S–C=O), 1678 (N–C=O); ^{1}H-NMR (DMSO-d_6): δ 3.62, 4.00 (2s, 2H, N–C$\underline{H}_2$–CO), 7.46–7.82 (m, 5H, Ar$\underline{H}$); *Anal*. Calcd for $C_{13}H_7N_3O_2S$ (269.28): C, 57.98; H, 2.62; N, 15.60. Found: C, 58.13; H, 2.78; N, 15.94.

5-(2-Fluorophenyl)-2,7-dioxo-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile (**6f**): Brownish red micro crystals; yield 62%; mp: 230–231°C; IR (KBr, cm^{-1}): 2900 (C–H aliphatic), 2210 (CN), 1700 (S–C=O), 1650 (N–C=O); ^{1}H-NMR (DMSO-d_6): δ 3.47, 3.51 (2s, 2H, N–C$\underline{H}_2$–CO), 7.23–7.79 (m, 4H, Ar$\underline{H}$); *Anal*. Calcd for $C_{13}H_6FN_3O_2S$ (287.27): C, 54.35; H, 2.11; N, 14.63; Found: C, 54.70; H, 2.26; N, 14.80; S, 8.10.

5-(2-Bromophenyl)-2,7-dioxo-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile (**6g**): Brownish yellow micro crystals; yield 60%; mp: 130–132°C; IR (KBr, cm^{-1}): 2970, 2881 (C–H aliphatic), 2229 (CN), 1743 (S–C=O), 1647 (N–C=O); ^{1}H-NMR (DMSO-d_6): δ 3.79, 4.10 (2s, 2H, N–C$\underline{H}_2$–CO), 7.33–7.80 (m, 4H, Ar$\underline{H}$); MS (EI) *m*/*z*: 348.15 (M+1, 0.19%), 349.05 (M+2, 3.69%), 270.15 (100%); *Anal*. Calcd for $C_{13}H_6BrN_3O_2S$ (348.17): C, 44.85; H, 1.74; N, 12.07; Found: C, 45.18; H, 1.88; N, 12.32.

5-(4-(Dimethylamino)phenyl)-2,7-dioxo-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile (**6h**): Yellow micro crystals; yield 72%; mp: 300–301°C; IR (KBr, cm^{-1}): 2935,2819 (C–H aliphatic), 2202 (CN), 1700 (S–C=O), 1651 (N–C=O); ^{1}H-NMR (DMSO-d_6): δ 2.94 (br, 6H, C$\underline{H}_3$–N–C$\underline{H}_3$), 3.60, 4.36 (2s, 2H, N–C$\underline{H}_2$–CO), 6.77–7.72 (m., 4H, Ar$\underline{H}$); ^{13}C-NMR (DMSO): δ 38.07 (2C), 59.12, 80.11, 110.96, 120.59 (2C), 124.84 (2C), 129.22 (2C), 151.24, 162.03, 172.11, 174.09; MS (EI) *m*/*z*: 312.00 (M^+, 32.25%), 148.40 (100%); *Anal*. Calcd for $C_{15}H_{12}N_4O_2S$ (312.35): C, 57.68; H, 3.87; N, 17.94. Found: C, 58.08; H, 3.97; N, 18.21.

Antitumor Screening Under a sterile condition, cell lines were grown in RPMI 1640 media (Gibco, NY, U.S.A.) supplemented with 10% fetal bovine serum (Biocell, CA, U.S.A.), 5×10^5 cell/mL was used to test the growth inhibition activity of the synthesized compounds. The concentrations of the compounds ranging from 0.01−100 μm were prepared in phosphate buffer saline. Each compound was initially solubilized in dimethyl sulfoxide (DMSO), however, each final dilution contained less than 1% DMSO. Solutions of different concentrations (0.2 mL) were pipetted into separate well of a microtiter tray in duplicate. Cell culture (1.8 mL) containing a cell population of 6×10^4 cells/mL was pippeted into each well. Controls, containing only phosphate buffer saline and DMSO at identical dilutions, were also prepared in the same manner. These cultures were incubated in a humidified incubator at 37°C. The incubator was supplied with 5% CO_2 atmosphere. After 48 h, cells in each well were diluted 10 times with saline and counted by using a coulter counter. The counts were corrected for the dilution.[19–22]

Antimicrobial Screening Antimicrobial activity was carried out using the disc diffusion technique according to Wiart. The newly synthesized compounds were diluted in DMSO with concentration 10 mg/mL, 6 mm filter paper Whatman no1 was soaked in 50 μL of each diluted compound. Both positive and negative control disc were applied using Tobramycin (10 μg/mL) and DMSO, respectively. The tested strains includes (*S. aureus* ATCC 25923, *E. coli* ATCC 25922, *Enterobacter aerogener* ATCC 23048, *Klebsiella* ATCC 23495, *Salmonella, Candida albican*).

Muller–Hinton agar was inoculated with microorganisms suspension that adjusted in its density to that of 0.5 McFarland standard. Within 15 min from preparation the adjusted suspension a sterile non toxic cotton swap on a wooden applicator was dipped into the standardized inoculums and rotates the soaked swab firmly against the upper inside wall of the tube to express excess fluid. Entire agar surface of the plate was streaked with the swab three times, turning the plate 60° angle between each streaking. Then the inoculated plate was allowed to dry before applying discs for five to fifteen minutes with lid in place. Discs containing the tested synthesized products were applied using aseptic technique on the surface of agar and plates were incubated immediately at 37°C for 14–19 h or later if necessary. The diameters of the measured zones showing complete inhibition were recorded to the nearest millimeter. The mean of the zone of inhibition was tabulated in Table 2.

Determination of the Minimum Inhibitory Concentration of the Synthesized Product MIC values of the synthesized compounds with *Staphylococcus aureus* ATCC 25923 were determined using broth dilution method. The tested compounds were dissolved in DMSO and further dilutions in Muller–Hinton broth were prepared to make 256, 128, 64, 32, 16, 8, 4, 2, 1 μg/mL . Both negative and positive control were prepared to ensure the sterility of the medium and viability of the tested strain respectively, also, a control test was carried out using inoculated broth with DMSO to test the solvent effect which was found to be inactive in culture medium. The results were represented in Table 3 and Fig. 4.

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