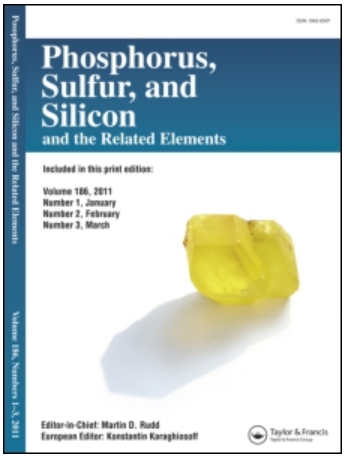

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Pyrimidinthiones (Part I): Utility of 2-Thioxopyrimidin-6-(1H)ones as Ring Transformer in the Synthesis of Fused Bi- and Tri-Cyclic Heterocyclic Compounds and Their Potential Biological Activities

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Pyrimidinthiones (Part I): Utility of 2-Thioxopyrimidin-6-(1H)ones as Ring Transformer in the Synthesis of Fused Bi- and Tri-Cyclic Heterocyclic Compounds and Their Potential Biological Activities

M. A. I. Salem, H. M. F. Madkour, M. I. Marzouk, M. E. Azab, and N. F. H. Mahmoud
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The pyrimidinethiones have wide biological and pharmaceutical activities, that have attracted considerable interest in recent years especially as antiviral inhibiting production of hepatitis B virus (HBV), and in vitro insulin-mimetic. Activity of the complexes of pyrimidinone derivatives evaluated from 50% inhibitory concentration promoted us to study the transformation of the 2-thioxopyrimidin-6(1H) ones to fused bi- and tri-cyclic heterocyclic compounds having the pyrimidine moieties and screening their biological activity.

*The reactivity of 2-mercapto-4-aryl-5-cyanopyrimidin-6(1H)ones (**1**) towards alkylation by different mono and bifunctional halo-organic compounds has been investigated to give S-monoalkylated products **2**,**7** and **9**; S- and N-dialkylated products **3**,**13** and **14**. Treatment of **1** and/or **2** with hydrazine hydrate as a nitrogen nucleophile have been investigated to give **4**, treatment of **4** with CS_2 and sodium nitrite in the presence of acetic acid (0°C) produced 1,2,4-triazolopyrimidin-5(1H)one derivatives (**5**)and tetrazolo[1,5-a]pyrimidin-5(1H)ones (**6**), respectively. Also cyclization of **7** and **9** gave [1,3]thiazolo[3,2-a]pyrimidin-5(1H)one and [1,3]thiazolo[3,2-a]pyrimidin-3,5-dione derivatives **8** and **10** respectively, treatment of **10** with aromatic aldehyde produces **11** which reacted with guanidine HCl to give pyrimido[4,5-d]thiazolo[3,2-a]pyrimidin-6(1H)one derivative **12**. Reaction of **14** with o-phenylenediamine was investigated and gave [1,4]quinoxalino[2,3-b][1,3]thiazolo[3,2-a]pyrimidin-9(1H)one derivative **15.***

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Keywords Biological activity; pyrimido[4,5-d]thiazolo[3,2-a]pyrimidinone; quinoxalino [2,3-b]thiazolo[3,2-a]pyrimidinone; tetrazolo[1,5-a] pyrimidinone; thiazolo[3,2-a]pyrimidinone

INTRODUCTION

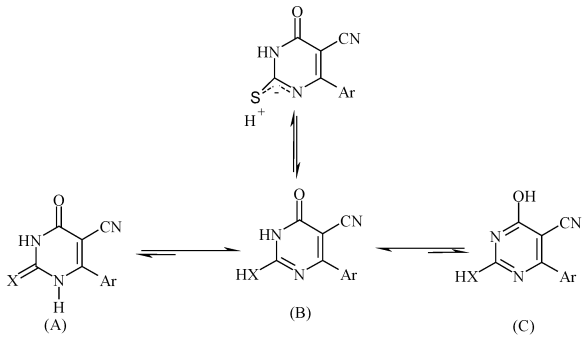
Recently pyrimidinthiones[1–7] have received much attention not only due to their unique physical and chemical properties[8,9] but also owing to their wide biological activities and reported medicinal applications[10] as anti-bacterial[11,12] anti-tumor,[8] anti-biotic,[13] anti-microbial,[14–16] anti-malarial[5] agents and as anti-thyroids[17]with potential medicinal interest.[18] On the other hand many pyrimidinthiones have properties potentially useful in stock or crops rising; as insecticides[19]also they are used in veterinary medicine.[20] This, together with our interest in the synthetic potential of fused hetero bi-and tri-cyclic systems,[21–27]encouraged us to investigate the synthesis of some fused cyanopyrimidinthiones of potential biological activity.

RESULTS AND DISCUSSION

Structurally pyrimidinone is closely related to pyridones, but the characteristic properties of pyridone are considerably enhanced in pyrimidinone owing to the presence of two electron-withdrawing ring nitrogen. When a hydroxyl group or an amino group is present in the pyrimidine moiety, the compound no longer behaves entirely as aromatic derivative, thus 2-thioxo(oxo and/or imino)-4-aryl-5-cyano-1,2,3,6-tetrahydropyrimidin-6-ones (**1**) exists in three major tautomeric forms (A), (B) and (C); the keto form (B) is the predominant one.[28] This phenomenon is confirmed by spectral data[29] in addition to our results of alkylation by mono and bi-functional halo-organic compounds which afforded S-monoalkylated products and/or S- and N-dialkylated products.

Reaction of 2-thioxo-4-aryl-5-cyano-1,2,3,6-tetrahydropyrimidin-6-ones (**1a**,**c**) with alkylating agents such as methyl iodide, allyl bromide and/or cyclohexyl bromide using 1:1 and 1:2 molar ratios in ethanolic NaOH afforded S-alkylated and/or S- and N-dialkylated products **2** and **3** respectively.

A few displacement reactions of the mercapto group in compounds (**1a**,**c**) were also investigated, thus treatment of compounds (**1a**,**c**) and/or **2a**,**b** with ammonium acetate by fusion and/or hydrazine hydrate (80%) in refluxing n-butanol yielded 2-imino-4-aryl-5-cyano-1,2,3,6-tetrahydropyrimidin-6-ones (**1e**,**g**) and/or 2-hydrazino-4-aryl-5-cyano-1,6-dihydropyrimidin-6-ones **(4a,b)** respectively, also



(1)

a) X = S, Ar = C_6H_3-(O–CH_2–O)-3,4

b) X = S, Ar = C_6H_3-(OCH_3)$_2$-2,4

c) X = S, Ar = C_6H_3-(OCH_3)$_2$-3,4

d) X = S, Ar = 

e) X = NH, Ar = C_6H_3-(O-CH_2-O)-3,4

f) X = NH, Ar = C_6H_3-(O-CH_3)$_2$-2,4

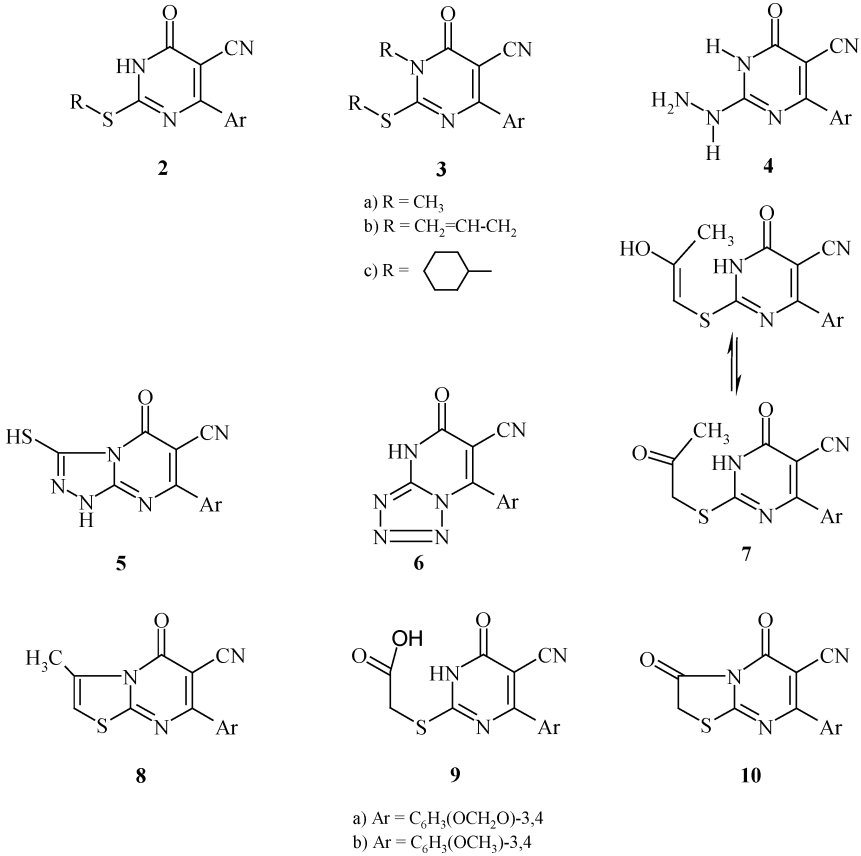
g) X = NH, Ar = C_6H_3-(O-CH_3)$_2$-3,4

cyclization of compound **4** via reaction of **4a** with CS_2 in presence of ethanolic KOH (10%), and also reaction of **4a**,**b** with $NaNO_2$ in presence of acetic acid at 0°C were carried out to afford 3-mercapto-6-cyano-7-(3,4-methylenedioxyphenyl)[1,2,4]triazolo[3,4-a]pyrimidin-5(1H)-one (**5**) and 7-cyano-8-(3,4-methylendioxylphenyl)tetrazolo[1,5-a]pyrimidin-6(5H)-one (**6a**,**b**) respectively.

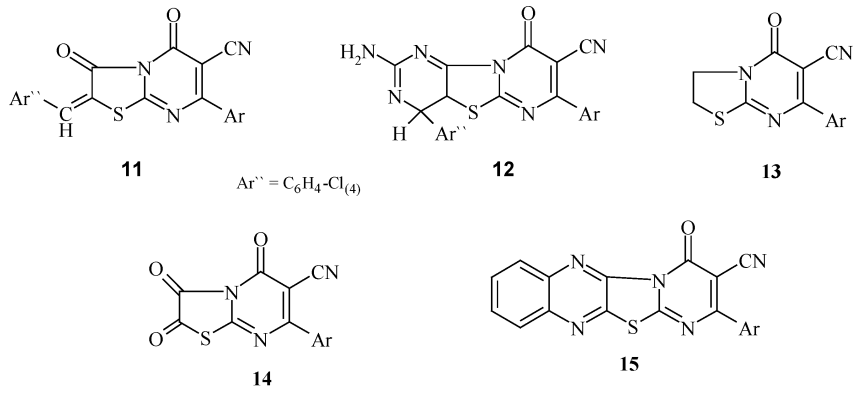
Alkylation of **1a** with α-haloketones such as mono-bromoacetone[8] depends upon the reaction conditions and the used base; if the reaction is carried out in refluxing ethanol and piperidine, the obtained products are 2-substituted thio-4-(3,4-methylenedioxyphenyl)-5-cyanopyrimidin-6(1H)-ones (**7**), while if it done in DMF and ethanolic NaOH (10%) it yielded 3-substituted 6-cyano-7-(3,4-methylenedioxyphenyl)-[1,3]thiazolo[3,2-a]pyrimidine-5-ones (**8**), also compounds (**7**) underwent cyclization by refluxing with a mixture of acetic anhydride/pyridine (1:1) to afford (**8**).

The products of alkylation of (**1a**,**c**) with α-haloacid and/or α-halo-ester such as mono-chloroacetic acid is dependent upon the reaction conditions[30]; if the reaction is carried out in refluxing ethanol/piperidine and/or dry acetone/anhydrous potassium carbonate, the isolated products are 4-aryl-5-cyanopyrimidin-6(1H)-one-2-thioglycollic acid derivatives (**9a**,**b**), while if it done in DMF and ethanolic NaOH (10%), the products are identified as the bicyclic

system 6-cyano-7-aryl[1,3]thiazolo[3,2-a]pyrimidin-3,5-dione derivatives (**10a**,**b**), which are obtained also on treatment of (**9a**,**d**) with a refluxing mixture of glacial acetic acid-anhydrous AcONa. On the other hand treatment of the title compounds (**1a**,**c**) with chloroacetyl chloride[9] as bi-functional halo-organic compound in DMF afforded the same products **10a**,**b**. The presence of an active methylene group in **10a** was established by its condensation with *p*-chlorobenzaldehyde in the presence of glacial acetic acid-anhydrous AcONa mixture[9] to afford 2[(*p*-chlorophenyl)methylene]-6-cyano-7-(3,4-methylenedioxyphenyl)-[1,3]thiazolo[3,2-a]pyrimidin-3,5-diones (**11**). Utilizing the arylidene derivative **11** in hetero- tricycle system synthesis, was via its reaction with guanidine HCl in n-butanol with a few drops of piperidine to afford1-(*p*-chlorophenyl)-3-amino-7-cyano-8(3,4-



SCHEME 1



a) Ar = $C_6H_3(OCH_2O)$-3,4
b) Ar = $C_6H_3(OCH_2)$2-3,4

SCHEME 2

methylenedioxyphenyl)-pyrimidino [4,5-d][1,3] thiazolo[3,2-a]pyrimidin-6(1H)-one (**12**).

The synthesis of 2,2,3,3-tetrahydro-6-cyano-7-aryl-[1,3]thiazolo[3,2-a] pyrimidin-5(1H)-ones (**13a**,**b**) was accomplished by reacting the title compounds (**1a,c)** with 1,2-dibromoethane in DMF and ethanolic NaOH (10%); also compounds (**13a**,**b**) were synthesized authentically in a one-pot reaction by reacting (**1a**,**c**) with 2-chloroethanol[8,31] with a mixture of acetic anhydride/pyridine (1:1).

On the other hand, treatment of equimolar amounts of **1a** with oxalyl chloride in THF at room temperature in the presence of triethylamine afforded 2,3-dihydro-6-cyano-7-(3,4-methylenedioxyphenyl) [1,3]thiazolo[3,2-a] pyrimidin-2,3,5-trione derivative (**14**) which is condensed with o-phenylene-diamine to produce 7-(3,4-methylenedioxyphenyl)-[1,4]quinoxalino[2,3-b] [1,3] thiazolo[3,2-a]pyrimidin-9(1H) -one (**15**) as hetero tricycle system.

The characterization of newly synthesized compounds 1–15 are listed in Table I, while the spectroscopic data[32] are listed in Tables II and III. Also the biological activities of some products are listed in Table IV.

EXPERIMENTAL

All melting points are uncorrected. The infrared absorption spectra were measured on a Pye Unicam SP 2000 Infrared spectrophotometer as KBr Wafer Technique. The G.C-mass spectra were determined on

TABLE I Physical Data of Compounds 1–15

Compd	m.p.°C (colour)	Solvent (yield, %)	M.F. m. wt.	Analysis calc./found C%	H%	N%	S%
1a	248-50	E	$C_{12}H_7N_3O_3S$	52.74	2.56	15.38	11.72
	(yellow)	(93.2)	273	52.69	2.59	15.30	11.65
1b	237-38	M	$C_{13}H_{11}N_3O_3S$	53.97	3.80	14.52	11.08
	(yellow)	(92.5)	289	53.99	3.74	14.46	11.01
1c	280-82	A	$C_{13}H_{11}N_3O_3S$	53.97	3.80	14.52	11.08
	(yellow)	(92)	289	53.90	3.84	14.49	11.12
1d	284-86	M	$C_9H_5N_3OS_2$	45.94	2.14	17.86	27.26
	(brown)	(76)	235	45.99	2.10	17.92	27.21
1e	> 360	E	$C_{12}H_8N_4O_3$	56.25	3.15	21.87	—
	(brown)	(70)	256	56.17	3.11	21.80	—
1f	232-34	E	$C_{13}H_{12}N_4O_3$	57.35	4.44	20.58	—
	(brown)	(73)	272	57.41	4.39	20.62	—
1g	240-42	E	$C_{13}H_{12}N_4O_3$	57.35	4.44	20.58	—
	(brown)	(70)	272	57.29	4.38	20.53	—
1h	312-14	M	$C_9H_6N_4OS$	49.53	2.77	25.67	14.69
	(brown)	(60)	218	49.60	2.71	25.71	14.63
2a	266-67	E	$C_{13}H_9N_3O_3S$	54.35	3.16	14.63	11.15
	(yellow)	(74)	287	54.43	3.12	14.58	11.20
2b	298-300	E	$C_{14}H_{13}N_3O_3S$	55.43	4.32	13.86	10.57
	(yellow)	(75)	303	55.51	4.40	13.80	10.62
2c	278-80	M	$C_{15}H_{11}N_3O_3S$	57.50	3.54	13.41	10.23
	(brown)	(58)	313	57.41	3.62	13.37	10.27
2d	251-52	Bz/E	$C_{18}H_{17}N_3O_3S$	60.83	4.82	11.82	9.02
	(brown)	(48)	355	60.75	4.79	11.88	9.10
3a	262-64	Bu	$C_{14}H_{11}N_3O_3S$	55.81	3.65	13.95	10.63
	(yellow)	(72)	301	55.98	3.15	14.23	10.35

(*Continued on next page*)

TABLE I Physical Data of Compounds 1–15 (*Continued*)

Compd	m.p.°C (colour)	Solvent (Yield, %)	M.F. m. wt.	Analysis calc./found C%	H%	N%	S%
3b	288-89	Diox.	$C_{15}H_{15}N_3O_3S$	56.77	4.76	13.24	10.10
	(yellow)	(68)	317	56.68	4.70	13.32	10.02
3c	220-21	E	$C_{18}H_{15}N_3O_3S$	61.18	4.28	11.89	9.07
	(brown)	(55)	353	61.24	4.22	11.84	9.12
3d	263-64	Bz/E	$C_{24}H_{27}N_3O_3S$	65.88	6.22	9.60	7.33
	(brown)	(46.5)	437	65.85	6.16	9.65	7.28
4a	240-42	B	$C_{12}H_9N_5O_3$	53.14	3.34	25.82	–
	(brown)	(68)	271	53.23	3.27	25.76	
4b	222-24	Bz	$C_{13}H_{13}N_5O_3$	54.35	4.52	24.39	- -
	(brown)	(65)	287	54.59	4.71	24.01	
5	262-64	B	$C_{13}H_7N_5O_3S$	49.89	2.23	22.36	10.32
	(yellow)	(75)	313	50.02	2.51	22.72	10.49
6a	166-67	Diox	$C_{12}H_6N_6O_3$	51.06	2.12	29.78	- -
	(pale brown)	(52)	282	50.98	2.09	29.82	
6b	148-49	Bz/E	$C_{13}H_{10}N_6O_4$	52.34	3.35	28.86	–
	(brown)	(58)	298	52.05	3.40	29.02	
7	118-20	Bz	$C_{15}H_{11}N_3O_4S$	54.71	3.34	12.76	9.72
	(brown)	(63)	329	54.64	3.42	12.85	9.79
8	290-91	E	$C_{15}H_9N_3O_3S$	57.87	2.89	13.50	10.29
	(brown)	(71)	311	58.04	3.12	13.12	10.57

9a	210-12	E	$C_{14}H_9N_3O_5S$	50.75	2.71	12.68	9.66
	(yellow)	(72)	331	50.93	2.35	12.89	9.27
9b	302-04	B	$C_{15}H_{13}N_3O_5S$	51.87	3.74	12.10	9.22
	(brown)	(69)	347	52.09	3.99	11.86	9.61
10a	281-82	Bz	$C_{14}H_7N_3O_4S$	53.67	2.23	13.41	10.22
	(pale yellow)	(64)	313	53.75	2.30	13.46	10.16
10b	309-311	Diox.	$C_{15}H_{11}N_3O_4S$	54.70	3.37	12.76	9.74
	(pale yellow)	(68)	329	54.62	3.30	12.72	9.81
11	218-19	Bu	$C_{21}H_{10}ClN_3O_4S$	57.86	2.29	9.64	7.34
	(brown)	(42)	435.5	57.43	2.07	9.38	7.78
12	264-66	E	$C_{22}H_{13}ClN_6O_3S$	55.40	2.72	17.62	6.71
	(colourless)	(54)	476.5	55.68	3.01	17.15	6.26
13a	186-87	M	$C_{14}H_9N_3O_3S$	56.15	3.01	14.04	10.70
	(colourless)	(46)	299	55.91	3.42	13.78	10.35
13b	238-39	Diox.	$C_{15}H_{13}N_3O_3S$	57.14	4.12	13.33	10.15
	(pale yellow)	(54)	315	57.69	4.57	13.80	9.94
14	262-64	Bu	$C_{14}H_5N_3O_5S$	51.38	1.54	12.84	9.80
	(yellow)	(58)	327	51.31	1.60	12.79	9.85
15	304-5	A	$C_{20}H_9N_5O_3S$	60.15	2.25	17.54	8.02
	(brown)	(28)	399	59.86	2.65	17.92	7.78

A = Acetic acid, Bu = n-Butanol, Bz = Benzene, Diox. = Dioxane, E = Ethanol and M = Methanol.

TABLE II Spectral Data of Compounds 1-15

Compd	IR (ν in cm^{-1})	^{1}H-NMR δ (ppm)	MS: m/z (abundance, %)
1a	$\nu_{OH/NH}$ (3162/3546), $\nu_{C\equiv N}$ (2230), $\nu_{C=O}$ (1708), $\nu_{C=N}$ (1635), $\nu_{C=C}$ (1605) and ν_{C-S} (1110)	DMSO-d_6: 13.8 & 13.16 (two s, 2H, 2NH), 7.28–7.13 (m, 3H, Ar-H) and 6.23 & 6.14 (two s, 2H, –O–CH_2–O)	275 ([M + 2]$^{+\cdot}$, 20), 274 ([M$^+$+ 1]$^+$, 100), 273 ([M]$^+$, 71.9), 272 (56.8), 245 (12.8), 216 (14.9), 214 (15.5), 186 (14.4), 170 (10.1), 121 (9%), 93(6.9) and 64 (13.7%)
1c	$\nu_{OH/NH}$ (3274), $\nu_{C\equiv N}$ (2225), $\nu_{C=O}$ (1680), $\nu_{C=N}$ (1640), $\nu_{C=C}$ (1600) and ν_{C-S} (1131)	13.14 (two s, 2H, 2NH), 7.38-7.14 (m, 3H, Ar-H) and 3.87 & 3.85 (two s, 6H, 2-OCH_3)	—
1d	$\nu_{OH/NH}$ (3192/3447), $\nu_{C\equiv N}$ (2223), $\nu_{C=O}$ (1676), $\nu_{C=N}$ (1636), $\nu_{C=C}$ (1595) and ν_{C-S} (1122)	13.28 & 12.9 (two s, 2H, two NH) and 6.62–5.41 (m, 3H, Ar-H)	—
2b	$\nu_{OH/NH}$ (3408/3457), $\nu_{C\equiv N}$ (2219), $\nu_{C=O}$ (1665), $\nu_{C=N}$ (1642) and $\nu_{C=C}$ (1605)	DMSO-d_6: 13.14 (s, 1H, NH–C=O), 7.65-7.16 (m, 3H, ArH), 4.0 & 3.89 (two s, 6H, 2–OCH_3) and 2.62 (s, 3H, S–Me)	288 (M–Me, 21.5), 287 (Me–MeH, 100), 273 (10.2), 241 (8.5), 214 (27.0) and 148 (15.5).
2c	$\nu_{OH/NH}$ (3448), $\nu_{C\equiv N}$ (2215), $\nu_{C=O}$ (1735), $\nu_{C=N}$ (1647) and $\nu_{C=C}$ (1605)	—	314 ([M]$^+$+ 1, 16%), 313 (M$^+$, 56.4), 312 (M$^+$ - 1, 100), 273 (23.1), 272 (17.7), 240 (9.6), 214 (27.3), 148 (44.2), 121 (6.0)
2d	$\nu_{OH/NH}$ (3452), $\nu_{C\equiv N}$ (2230), $\nu_{C=O}$ (1710), $\nu_{C=N}$ (1640) and $\nu_{C=C}$ (1600)	12.8 (s, 1H, NH–C=O), 7.56-7.28 (m, 3H, Ar–H), 6.25 & 6.13 (two s, 2H, OCH_2–O) and 3.12–2.54 (m, 11H, cyclic-H)	—
3b	$\nu_{C\equiv N}$ (2228), $\nu_{C=O}$ (1685), $\nu_{C=N}$ (1640) and $\nu_{C=C}$ (1610) and νc-s (1145)	DMSO-d_6: 7.68-7.12 (m, 3H, Ar–H), 4.06 & 3.83 (two, s, 6H, 2 –OCH_3), 3.25 (s, 3H, CH_3–N–C=O) and 2.63 (s, 3H, –S–CH_3).	317 (M]$^+$, 7.7), 303 (17.3), 288 (25.8), 287 (100), 271 (6.3), 227 (6), 201 (35.5), 200 (9.7), 187 (36.5) and 155 (8.3)
3c	$\nu_{C\equiv N}$ (2222), $\nu_{C=O}$ (1678), $\nu_{C=N}$ (1632), $\nu_{C=C}$ (1605) and ν_{C-S} (1130)	DMSO-d_6: 11.62 (br s, 1H exchangeable C=NH), 7.54–7.18 (m, 3H, Ar–H), 6.79-6.45 (br, m, 3H, NH–NH_2) and 6.23 & 6.18 (two s, 2H, –O–CH_2–O)	257 (M–Me], 100), 256 (51.6), 241 (26.6), 214 (35.3), 186 (17.2), 148 (68.8), 121 (11.1), 118 (19.5), 76 (11.1), 63 (35.6) and 50 (20.4).
5	ν_{NH} (3380), $\nu_{C\equiv N}$ (2218), $\nu_{C=O}$ (1682), $\nu_{C=N}$ (1625) and $\nu_{C=C}$ (1595), and νc-s (1175)	DMSO-d_6: 7.38-7.22 (m, 3H, Ar–H), 6.79 (s, 1H, NH), 6.27 (s, 2H, –O–CH_2–O) and 4.73 (s, 1H, SH)	—

6a	$\nu_{OH/NH}$ (3377-br), $\nu_{C\equiv N}$ (2224), $\nu_{C=O}$ (1672), $\nu_{C=N}$ (1620) and $\nu_{C=C}$ (1596)	DMSO-d6: 7.67-7.21 (m, 3H, ArH), 6.10 (s, 2H, –O–CH_2–O) and 3.25 (br s, 1H, exchangeable NH OH)	—
7	$\nu_{OH/NH}$ (3355), $\nu_{C\equiv N}$ (2218), $\nu_{C=O}$ (1726), $\nu_{C=O}$ (1673), $\nu_{C=N}$ (1642) and $\nu_{C=C}$ (1614)	—	329 (M^+, 5.5), 314 (6.7), 313 (21.1), 287 (6.3), 200 (52.3), 171 (12.7), 170 (96.1), 116 (16.8), 115 (10.7) and 114 (100)
8	$\nu_{C\equiv N}$ (2216), $\nu_{C=O}$ (1695), $\nu_{C=N}$ (1635) and $\nu_{C=C}$ (1605) and νc-s (1145)	(DMSO-d_6) 4.63 (s, 1H,S–CH=C), 6.18 (s, 2H, –O–CH_2–O) and 8.07–7.29 (m, 8H, Ar–H)	—
10a	$\nu_{OH/NH}$ (3449/3419), $\nu_{C\equiv N}$ (2228), $\nu_{C=O}$ (1685), $\nu_{C=O}$ (1665), $\nu_{C=N}$ (1625) and $\nu_{C=C}$ (1605)	(DMSO-d_6) 11.82 (s, 1H, OH), 7.48-7.13 (m, 4H, Ar–H & S–CH=C) and 6.16 (s, 2H, O–CH_2–O)	313 (M, 4.4), 286 (6.4), 285 (21.6), 178 (100), 173 (14.0), 148 (31.0), 135 (66.2), 77 (11.8) and 51 (9.2)
11	$\nu_{OH/NH}$ (3380), $\nu_{C\equiv N}$ (2218), $\nu_{C=O}$ (1710), $\nu_{C=O}$ (1685), $\nu_{C=N}$ (1640), $\nu_{C=C}$ (1610) and ν_{C-S} (1170)	(DMSO-d_6) 7.82 (s, 1H, C=CHAr‘), 7.38-7.18 (m, 7H, Ar–H) and 6.22 (s, 2H, –O–CH_2–O)	—
12	ν_{NH2} (3420), $\nu_{C\equiv N}$ (2224), $\nu_{C=O}$ (1685), $\nu_{C=N}$ (1635), $\nu_{C=C}$ (1610) and ν_{C-S} (1170)	(DMSO-d_6) 7.42–7.24 (m, 7H, Ar–H), 6.24 (s, 2H, O–CH_2–O), 5.58 (br, s, 2H, NH_2), 3.84-3.78 (d, 1H, Ar–CH–N=C, J = 7.8) and 3.38-3.34 (d, 1H, CH–S, J = 6.2)	—
13a	$\nu_{C\equiv N}$ (2221), $\nu_{C=O}$ (1680), $\nu_{C=N}$ (1640), $\nu_{C=C}$ (1595) and ν_{C-S} (1172)	(DMSO-d_6) 7.48-7.28 (m, 3H, Ar-H), 6.18 (s, 2H, –O–CH_2-O-), 3.82 (t, 2H, -S-CH_2-) and 3.33 (t, 2H, N-CH_2)	—
13b	$\nu_{C\equiv N}$ (2218), $\nu_{C=O}$ (1685), $\nu_{C=N}$ (1625), $\nu_{C=C}$ (1590) andν_{C-S} (1175)	(DMSO-d_6) 7.5-7.2 (m, 3H, Ar-H)3.85 (s,6H,two OCH_3) 3.6(t,2H,S-CH_2)and 3.3 (t,2H,NH_2)	—
14	$\nu_{C\equiv N}$ (2232), $\nu_{C=O}$ (1750) (1695), $\nu_{C=O}$ (1680), $\nu_{C=N}$ (1630) and $\nu_{C=C}$ (1608)	(DMSO-d_6) 7.52-7.23 (m, 3H, Ar-H) and 6.21 (s, 2H, -O-CH_2-O-)	257 (M-C_2O_3]$^+$), 252 (24), 149 (51.2), 136 (18.7), 121 (7.9), 119 (3.4), 102 (6.8), 91 (11.7), 86 (28.1), 64 (7.9), 38 (41.5), 36 (100)
15	$\nu_{C\equiv N}$ (2230), $\nu_{C=O}$ (1675), $\nu_{C=N}$ (1632), $\nu_{C=C}$ (1605) andν_{C-S} (1173)	(DMSO-d_6) 7.74–7.28 (m, 7H, Ar-H) and 6.24 (s, 2H, -O-CH_2-O-)	—

TABLE III ^{13}C-NMR Data for the Newly Synthesized Compounds

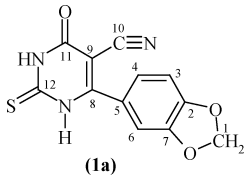
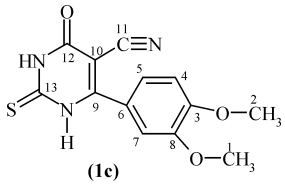
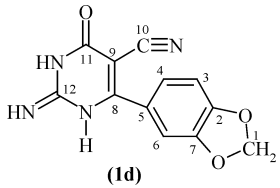
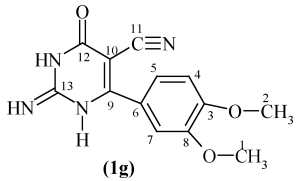
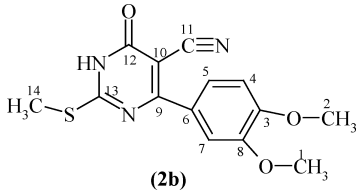
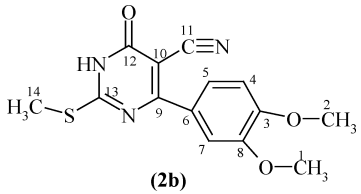
Structure	^{13}C-NMR
 **(1a)**	106.16 (C_1), 138.9 (C_2), 130.20 (C_3) 132.1 (C_4), 132.1 (C_5), 130.2 (C_6), 137.39 (C_7), 156.4 (C_8), 110.7 (C_9), 117.6 (C_{10}), 161.2 (C_{11}) and 155.6 (C_{12})
 **(1c)**	55.5 (C_1), 56.0 (C_2), 163.5 (C_3) 131.1 (C_4), 133.6 (C_5), 133.6 (C_6), 131.1 (C_7), 159.8 (C_8), 152.8 (C_9), 112.2 (C_{10}), 116.9 (C_{11}) 161.2 (C_{12}) and 155.6 (C_{13})
 **(1d)**	105.92 (C_1), 138.62 (C_2), 129.6 (C_3) 131.8 (C_4), 131.8 (C_5), 129.6 (C_6), 137.4 (C_7), 143.4 (C_8), 111.6 (C_9), 114.2 (C_{10}), 160.1 (C_{11}) and 123.1 (C_{12})
 **(1g)**	55.1 (C_1), 55.7 (C_2), 163.3 (C_3) 132.6 (C_4), 133.8 (C_5), 133.8 (C_6), 142.8 (C_7), 161.7 (C_8), 142.8 (C_9), 111.8 (C_{10}), 116.2 (C_{11}), 159.8 (C_{12}) and 121.9 (C_{13})
 **(2b)**	56.1 (C_1), 54.9 (C_2), 162.8 (C_3) 131.8 (C_4), 134.6 (C_5), 134.6 (C_6), 131.8 (C_7), 161.7 (C_8), 154.9 (C_9), 112.2 (C_{10}), 117.8 (C_{11}), 158.7 (C_{12}), 162.6 (C_{13}) and 30.4 (C_{14})
 **(2b)**	107.2 (C_1), 138.2 (C_2), 131.97 (C_3), 131.5 (C_4), 131.5 (C_5), 131.97 (C_6), 137.6 (C_7), 153.5 (C_8), 113.7 (C_9), 118.2 (C_{10}), 166.2 (C_{11}), 64.8(C_{12}) and 160.4 (C_{13})

TABLE IV Biological Activity of the Newly Synthesized Compounds

	Inhibition							
	Asperigillus		Candida		E-Coli		St. aur	
Compd no.	A*	MIC	A*	MIC	A*	MIC	A*	MIC
1a	+	100	+	100	—	—	—	—
1c	+	100	+	100	++	50	++	50
1d	+	100	+	100	+++	25	+++	25
2a	—	—	—	—	+	100	+	100
2c	+	100	—	—	+	100	+	100
4b	+	100	—	—	++	50	++	40
5	+	100	+	100	—	—	—	—
6a	—	—	—	—	+++	25	++	25
7	—	—	—	—	++	50	++	50
8	+	100	+	100	++	50	++	50
9a	+	100	+	100	++	50	++	50
10b	+	100	+	100	++	50	++	50
11	++	50	++	50	+	100	+	100
12	+	100	—	—	+	50	—	—
14	—	—	—	—	+	100	+	100
15	++	50	++	50	+++	25	+++	25

The width of the zone of inhibition indicates the potency of antibacterial activity; (−) no antibacterial activity; (+) mild activity with the diameter of the zones equal to 0.6−0.8 cm; (++) moderate activity with the diameter of the zones equal to 1.2-1.3 cm; (+ + +) marked activity with the diameter of the zones equal to 1.8–1.2 cm. E. coli is Gram-negative and St. aur is a gram-positive bacteria and Asperigllus flavus and Candida albicans as fungi.[38–40]

AE1 MS.902 mass spectrometer, while the mass fragmentations were scanned on Shimadzu MS-1000 Ex instruments. The ^{1}H NMR spectra were determined on a Varian Gemini 200 and 400 NMR spectrophotometer using DMSO-d_6 and $CDCl_3$ as solvents, (chemical shifts in δ, ppm) and TMS as internal standard. Characterization data of the new synthesized products are given in Table I.

Reaction of Arylidene Ethyl Cyanoacetate with Thiourea, and/or Guanidine Hydrochloride; Formation of 1a-h

The appropriate arylidene ethyl cyanoacetate (2.7 g, 0.01 moles) was condensed with thiourea (0,6 g, 0.01 moles), and/or guanidine hydrochloride (0.95 g, 0.01 moles) in the presence of sodium ethoxide (0.23 g of sodium metal in 10 mL of absolute ethanol). The reaction mixture was heated under reflux for 4 h, then cooled and poured onto ice/HCl. The solid, which separated out, was filtered off, dried and

recrystallized yielding the products **1a**–**h**. Some of the products were previously prepared by other methodologies[33–37] (Table I).

Reaction of 1a, c with Methyl Iodide, and/or 1a with Allyl Bromide and Cyclohexyl Bromide; Formation of 2a–d

An equimolar mixture of **1a**,**c** (2.7 g, 0.01 moles) and methyl iodide (1.4 g, 0.01 moles) and/or **1a** (2.7g, 0.01 moles) with allylbromide (1.2 g, 0.01 moles) & cyclohexyl bromide (1.6 g, 0.01 moles) in ethanolic sodium hydroxide 10% (2.5 g NaOH in 25 mL EtOH 96%) was refluxed for 1 h, the reaction mixture was cooled and neutralized by pouring onto ice/HCl. The precipitated solid was collected by filtration, washed with water, dried and crystallized affording **2a**-**d** respectively (Table 1).

Reaction of 1a, c with Methyl Iodide and/or 1a with Allyl Bromide and Cyclohexyl Bromide; Formation of 3a–d

A mixture of **1a**, **c** (2.7 g, 0.01 moles) and organohalo compounds namely methyl iodide (1.4 g, 0.02 moles), and/or **1a** (2.7 g, 0.01 moles) with allyl bromide (1.2 g, 0.02 moles) and cyclohexyl bromide (1.6 g,0.02 moles) in alcoholic sodium hydroxide 20% (5 g of NaOH in 25 mL EtOH) was heated under reflux for 2 h. The reaction mixture was left to cool, acidified by cold HCl (2N) after pouring onto ice; the solid that separated out was filtered by suction and recrystallized to give **3a–d** respectively.

Action of Ammonium Acetate on 2a–d; Formation of 1e, g

The mixture of 2a-b (2.09 g, 0.01 moles) and ammonium acetate (2.31 g, 0.03 moles) was fused at a temperature of not more than 210°C for 2 h, cooled, washed well with water several times and collect the solid that separated out by filtration, followed by recrystallisation to furnish the products named **1e**,**g** respectively.

Preparation of Authentic Sample

The fusion of pryimidine derivatives **1a**,**c** (2.7 g,0.01 moles) with ammonium acetate (0.03 mol, 2.31 g) at temperature not more than 200°C for 2 h afforded the authentic products **1e**,**g** which were identified by m.p., mixed m.p., I.R. comparison and TLC.

Reaction of 1a, c and/or 2a, b with Hydrazine Hydrate; Formation of 4a, b

To a solution of **1a**,**c** (2.7 g, 0.01 moles) and/or **2a**,**b** (2.09 g, 0.01 moles) in n-butanol (30 mL), hydrazine hydrate (80%) (0.02 mol; 1.0 mL) was added and the reaction mixture was heated under reflux for 6 h, most of the solvent was distilled off using a rotatory evaporator and left to cool. The solid product that deposited was collected by filtration, washed with water, dried and then recrystallized to give the monohydrazino derivative **4a**,**b** respectively.

Action of Carbon Disulphide on 4a; Formation of 5

A mixture of **4a** (2.71 g, 0.01 moles, in 25 mL ethanol) and ethanolic solution of potassium hydroxide (1 g/10 mL H_2O and 25 mL ethanol) was stirred at room temperature for 1 h, then carbon disulphide (2 mL) was added drop wise with continuous stirring for additional 1 h. The reaction mixture was heated under reflux on water bath for 6 h followed by concentrating the resultant solution to its half volume using a rotatory evaporator. The reaction mixture was left to cool at room temperature then kept overnight in the refrigerator. The solid that separated out was filtered off, dried, washed with L.P 60-80°C several times and then recrystallized to afford the desired product **5**.

Action of Nitrous Acid ($NaNO_2$/AcOH) on 4a, b; Formation of 6a, b Respectively

Hydrazino derivatives **4a,b** (2.7 g, 0.01 moles) was dissolved in acetic acid (30 mL) and the solution was cooled to 0°C in an ice/salt bath then an aqueous solution of sodium nitrite (0.8 g) in water (10 mL) was added simultaneously with stirring, the reaction mixture was left at 0°C with additional stirring for another 3 h. The reaction mixture was kept overnight in a refrigerator, then poured onto ice/water. The solid that collected by filtration was crystallized from the proper solvent to afford **6a**,**b** respectively.

Reaction of 1a with Bromoacetone; Formation of 7

When compound **1a** (2.7 g , 0.01 moles) was allowed to react with monobromoacetone (1.36 g, 0.01 moles) in cold ethanol (30 mL), a few drops of piperidine (1 mL) was added during stirring for 30 min. at room temperature, then the mixture was refluxed for 6 h. The volume of the mixture was reduced to half, and then it was left to cool, poured onto

ice/HCl. The solid product that precipitated was filtered off, dried, and then recrystallized to give the product **7**.

Reaction of Pyrimidine 1a with Bromoacetone; Formation of 8

A solution of **1a** (2.7 g, 0.01 moles) in dimethyl formamide (30 mL) was immersed in ice, then bromoacetone (5.6 g, 0.01 moles) was added drop wise with vigorously stirring during 30 min. ethanolic sodium hydroxide 10% (2.5 g NaOH in 25 mL ethanol) also was added drop wise with continuous stirring for additional 30 min. The reaction mixture was heated under reflux for 3 h, most of the solvent was distilled off and left to cool, poured onto ice/HCl and the solid product that separated out was filtered off, dried and recrystallized to yield the products **8**, respectively.

Cyclization of 7: Formation of 8

A mixture of compound **7** (3.29 g, 0.01 moles) in 50 mL of acetic anhydride –dry pyridine mixture (1:1) was heated under reflux for 6 h., then the reaction mixture was cooled followed by dilution with ice/water. The solid that obtained was filtered off, dried and recrystallized to afford the cyclized product **8**, respectively, which were identified by m.p., and mixed m.p., IR comparison and TLC.

Reaction of 1a, c with Chloroacetic Acid; Formation of 9a, b

An equimolar mixture of **1a**,**c** (2.7g, 0.01 moles) and chloroacetic acid (0.95 mL, 0.01 moles) in ethanol (30 mL) and piperidine (1 mL) was added, and then the reaction mixture was heated under reflux for 6 h. The reaction mixture was concentrated to its half volume, left to cool and pour onto ice/HCl. The solid that separated out was recovered by filtration and recrystallized to yield the thioglycollic acid derivatives **9a**,**b**, respectively.

Reaction of 1a, c with Chloroacetic Acid; Formation of 10a, b

An equimolar mixture of **1a**,**c** (2.7 g, 0.01 moles) and mono-chloroacetic acid (0.95 mL, 0.01 moles) in dimethyl formamide (30 mL) was stirred at room temperature for 30 min. Ethanolic sodium hydroxide 10% (2.5 g NaOH in 25 mL ethanol) was added with good stirring for another 30 min., then the reaction mixture was heated under reflux for 6 h. The volume of the mixture was reduced to half using a rotatory evaporator

followed by cooling; the reaction mixture was neutralized by pouring onto ice/HCl. The solid that separated out was recovered by filtration and recrystallized to yield the cyclic adducts **10a**,**b**, respectively.

Authentic Proofs for the Formation of 10a, b

Cyclization of 9a, b; Formation of 10a, b

A mixture of **9a**,**b** (3.3 g, 0.01 moles), glacial acetic acid (30 mL) and anhydrous sodium acetate (freshly prepared; 2 g) was refluxed for 4 h., cooled and/then poured onto crushed-ice, to yield the solid products **10a**,**b**, respectively.

Reaction of Pyrimidine 1a, c with Chloroacetyl Chloride; Formation of 10a,b

The solution of **1a**,**c** (2.7 g, 0.01 moles) in dimethylformamide (30 mL) was heated under reflux for 6 h with chloroacetyl chloride (1.13 mL, 0.01 moles). The reaction mixture was left to cool after evaporization most of the solvent. The solid product that precipitated down was filtered off, dried and recrystallized to afford the desired products **10a**,**b**, respectively.

The desired products **10a**,**b** either from method A or B were identified by m.p., mixed m.p., IR comparison and TLC.

Reaction of 10a with p-Chlorobenzaldehyde; Formation of 11

A mixture of **10a** (3.1 g, 0.01 moles), p-chlorobenzaldehyde (1.4 g, 0.01 moles) and anhydrous sodium acetate (2 g) in glacial acetic acid (30 mL) was heated under reflux for 6 h, cooled, then poured onto crushed ice. The resultant solid was filtered off, dried and recrystallized to yield **11**.

Reaction of 11 with Guanidine Hydrochloride; Formation of 12

A mixture of an equimolar amount of **11** and guanidine hydrochloride in n-butanol (40 mL) with few drops of piperidine (0.5–1.0 mL) was stirred at room temperature for 30 min. followed by heating under reflux with continuous stirring for 6 h. The reaction mixture was concentrated to its half volume. The separated solid was filtered off, dried and recrystallized to give **12** as the only product.

Reaction of 1a, c with 1,2–dibromoethane; Formation of 13a, b

A mixture of **1a**,**c** (2.7 g, 0.01 moles) and 1,2-dibromoethane (0.01 mol) and ethanolic NaOH 10% (2.5 g NaOH in 25 mL ethanol) in dimethyl formamide (40 mL) was heated under reflux for 4 h. The reaction mixture was concentrated to its half volume, then left to cool, poured onto ice/HCl to acidify the solution. The solid that separated out was filtered off, washed, dried and recrystalized to yield the products **13a, b**, respectively.

Synthesis of 13a, b Authentically

In one-pot reaction a mixture of **1a**,**c** (2.7 g, 0.01 moles) and 2-chloroethanol (0.8 g, 0.01 moles) in dry pyridine (20 mL) was stirred for 1 h at room temperature, then 40 mL of dry pyridine/acetic anhydride mixture (1:1) was added, stirring was continued for another 1 h at room temperature. The reaction mixture was refluxed for 6 h, concentrated to its half volume, cooled and neutralized by conc HCl then poured onto crushed ice. The solid products obtained were identified to be **13a, b** respectively by m.p., mixed m.p., IR comparison and TLC.

Reaction of 1a with Oxalyl Chloride; Formation of 14

A solution of **1a** (2.73 g, 0.01 moles) in least amount of dry tetrahydrofuran (15 mL) and triethyl amine (1-2 mL) was stirred at room temperature for 10 min. then the solution of oxalyl chloride (1.27 g, 0.01 moles) in dry tetrahydrofuran (15 mL) was cooled by immersing in ice for 10 min. then it was added drop wise during 30 min. with stirring. The mixture was stirred for additional 4 h and then left overnight. The solid product that precipitated down was collected by filtration and recrystallized to afford **14**.

Reaction of 14 with o-Phenylenediamine; Formation of 15

A mixture of **14** (3.2 g, 0.01 moles), o-phenylene diamine (1.1 g, 0.01 moles) and anhydrous $ZnCl_2$ (3 g) was mixed well then fused at 140–150°C for 2 h. The desired product **15** was obtained after pouring the reaction mixture over hot water, washing with water several times during the filtration process and recrystallization.

CONCLUSION

Bi- and tri-acyclic heterocyclic compounds having the pyrimidine moieties are an important class of compounds in medicinal chemistry.

From Table III it can be seen that compounds **1d**, **6a**, and **15** were the most effective against both gram-negative and gram-positive bacterial strains whereas some other compounds have moderate effect on the tested bacteria, while compounds **11b** and **15** were the most effective against the test fungi. We can conclude that compounds **1d**, **6a**, **15** can be used as antibacterial agents both gram-negative and gram-positive bacteria, while compounds **11b**, and **15** can be used as moderate antifungal agents against Asperigillus flavus and Candida albicans.

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