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Behaviour of 4,6-Diaryl-2(1H) pyrimidine-2-thiones Towards Some Electrophiles and Nucleophiles

Nadia T.A. Dawood*, Nahed F. Abdel-Ghaffar and Fekria M.A. Soliman

Department of Chemistry, Faculty of Science "Girls", Al-Azhar University, Cairo, Egypt.

4,6-DIARYl-1,2-dihydro-2(1*H*)-pyrimidine-2-thiones (1*a*,*b*) were used for the synthesis of several new pyrimidine derivatives. They were further subjected to hetero ring anellation affording isoxazolo [4,5-*d*] thiazolo [2,3-*a*] pyrimidine (5,6) and isoxazolo [4,5-*d*] thiazino [2,3-a] pyrimidines (11,12) . Biological evaluation of some of the prepared compounds revealed promising antimicrobial activity.

Keywords: Pyrimidinethione, Pyrimidothiazine, Thiazolopyrimidine and Antimicrobial activity.

It is well known that pyrimidine and fused pyrimdine heterocycles are of great biological interest, especially as antiviral, antimicrobial[1-8] and antitumor agents[9]. It has been shown[3,10] that some pyrimido-thiazine and thiazolopyrimidine derivatives exhibited marked antibacterial activity against some gram-positive bacteria strains. Also, some thiazolopyrimidines were tested for their anti-inflammatory activity and exerted a moderate effect [4]. In conjunction with our previous work on the synthesis of pyrimidinethione derivatives for biological evaluations [11-16] , we report herein on the synthesis of a series involving the pyrimidine-2-thione moiety and screening of the antimicrobial activity of some of the new derivatives.

Experimental

All melting points were measured in capillary tubes using an electro-thermal GallenKamp apparatus and are uncorrected. The IR spectra were recorded from KBr pellets on a Pye Unicam SP 3-300 spectrophotometer. The ^{1}H-NMR spectra were run on a Varian Gemini NMR spectrometer in deuterated dimethylsulfoxide (DMSO-d6) or deuterated chloroform ($CDCl_3$) at 300MHz using tetramethyl silane (TMS) as internal reference and results are expressed as δ values ppm. The mass spectra were performed on a Shimadzu GCMS-QP 1000 Ex mass spectrometer at 70 eV. The elemental analysis was carried out at the Micoanalytical Center of Cairo University.

Compounds 1*a*, 1*b* have been prepared as previously reported [11].

*E-mail: dawoudnadia@yahoo.com.

Reduction of 4,6-diaryl-1,2- dihydro pyrimidine-2-thione: Formation of 4,6-diaryl -1,2,3,4-tetrahydropyrimidine-2-thiones (2a, 2b)

To a suspension of compounds 1*a* or 1*b* (0.01 mol) in glacial acetic acid was added stepwise Zn dust (0.02 mol) in portions while stirring for half an hour at room temperature. After completion, the reaction mixture was diluted with water, filtered off, washed well with dilute ethanol and recrystallised from ethanol to give compounds 2*a*, 2*b* as white and pale yellow crystals, respectively (Table 1).

Reaction of 2a, 2b with chloroacetic acid: Formation of 5, 7-diaryl—2,3-dihdro-5H-thiazolo[3,2-a]pyrimidin-3-ones (3a,3b)

A mixture of compound 2*a* or 2*b* (0.01mol), chloroacetic acid (0.01mol) and freshly fused sodium acetate (0.05 mol) in glacial acetic acid –acetic anhydride mixture (30ml, 2:1) was refluxed for 4hr. After cooling, the reaction mixture was diluted with water and the product was collected, washed well with water and dilute alcohol then recrystallized from ethanol to give 3*a*, 3*b*, respectively (Table 1).

Reaction of 3a,b with aromatic aldehydes:Formation of 5, 7-diaryl-2-(arylmethylene)-2, 3-dihdro-5H-thiazolo[3,2-a]pyrimidin-3-ones (4a-f)

A mixture of compound 3*a* or 3*b* (0.01 mol), aromatic aldehydes namely, furfural, thiophene-2-aldehyde, isonicotinaldehyde or benzaldehyde (0.01 mol) and freshly fused sodium acetate (0.005 mol) in glacial acetic acid-acetic anhydride mixture (30 ml, 2:1) was refluxed for 3hr. After cooling, it was poured into water and the precipitate formed was collected, washed well with water, then dilute ethanol and recrystallized from the proper solvent to give 4*a*-4*f*, respectively (Table 1).

Reaction of 4a,d with hydroxylamine hydrochloride :Formation of 3,6,8-triaryl-2,3-dihydro-8H-isoxazolo[5`,4`:4,5]thiazolo[3,2a]pyrimidines (5a,5b)

A mixture of compound 4*a* or 4*d* (0.01mol), hydroxylamine hydrochloride (0.01 mol) and freshly fused sodium acetate (0.05 mol) in 30 mL of glacial acetic acid was refluxed for 6h. After cooling, it was poured into water and the precipitate formed was collected, washed well with water, then with dilute ethanol and recrystallised from the proper solvent as *5a*, 5*b*, respectively (Table 1).

Reaction of 5b with 2-chloroethyl methyl ether: Formation of 6-(4- bromophenyl)-2-(2-methoxyethyl) -8- phenyl-3- (2-thienyl) -2,3-dihydro- 8H- isoxazolo [5`,4`:4,5] thiazolo[2,3-a]pyrimidine (6)

A mixture of compound *5b* (0.01 mol) and sodium hydride (0.01 mol) in 25 ml of DMF was stirred on a steam-bath (adjusted at 70ºC) for 2 hr and then 2-chloroethyl methyl ether (0.01 mol) was added. Stirring was continued at 70ºC for 24 hr. The excess solvent was evaporated (reduced pressure) and the product was triturated with light petrol then recrystallized from the proper solvent to give 6 (Table 1).

TABLE 1.

Compd. No.	M.P.°C solvent of cryst.	Yield %	Molecular formula (Mol. wt.)	Analysis			Calcd/found%		
				C	H	N	S	Cl	Br
2a	205.206 EtOH	65	$C_{16}H_{13}SN_2Cl$ (300.5)	63.89 63.9	4.32 4.3	9.31 9.3	10.64 10.7	11.81 11.8	
2b	189-190 EtOH	72	$C_{16}H_{13}SN_2Br$ (345)	55.65 55.7	3.76 3.8	8.11 8.1	9.27 9.3		23.18 23.2
3a	223-224 EtOH	60	$C_{18}H_{17}OSN_2Cl$ (340.5)	63.43 63.4	3.81 3.8	8.22 8.2	9.39 9.4	10.42 10.4	
3b	215-216 EtOH	65	$C_{18}H_{13}OSN_2Br$ (385)	56.103 56.1	3.37 3.4	7.27 7.3	8.31 8.3		20.77 20.8
4a	231-232 B	64	$C_{23}H_{15}O_2SN_2Cl$ (418.5)	65.94 65.9	3.58 3.6	6.69 6.7	7.64 7.6	8.48 8.5	
4b	177-178 B	67	$C_{23}H_{15}OS_2N_2Cl$ (434.5)	63.52 63.5	3.45 3.5	6.44 6.4	14.72 14.7	8.17 8.2	
4c	199-200 B-P.E.	62	$C_{23}H_{15}O_2SN_2Br$ (463)	59.61 59.6	3.23 3.2	6.04 6.1	6.91 9.6		17.27 17.3
4d	213-214 EtOH	69	$C_{23}H_{15}OS_2N_2Br$ (479)	57.62 57.5	3.13 3.1	5.84 5.8	13.36 13.4		16.701 16.7
4e	183-184 P.E.	60	$C_{24}H_{16}OSN_3Br$ (474)	60.75 60.8	3.37 3.4	8.86 8.9	6.75 6.8		16.87 16.9
4f	235-236 B	83	$C_{25}H_{17}OSN_2Br$ (473)	63.42 63.4	3.59 3.6	5.91 5.9	6.76 7.8		16.91 16.9
5a	260-261 AcOEt	60	$C_{23}H_{16}O_2SN_3Cl$ (433.5)	63.66 63.7	3.69 3.7	9.68 9.7	7.38 7.4	8.18 8.2	
5b	231-232 AcOH	65	$C_{23}H_{16}OS_2N_3Br$ (494)	55.87 55.9	3.23 3.2	8.5202 8.5	12.95 13.0		16.19 16.2
6	197-198 P.E.	59	$C_{26}H_{22}O_2S_2N_3Br$ (552)	56.52 56.5	3.98 4.0	7.608 7.6	11.59 11.6		14.49 14.5
7a	286-287 AcEt	65	$C_{19}H_{19}OSN_2Cl$ (358.5)	63.59 63.6	5.29 5.3	7.81 7.8	8.92 8.9	9.902 9.9	
7b	252-253 $CHCl_3$	72		56.57 56.6	4.71 4.7	6.94 6.9	7.94 7.9		19.85 19.9

TABLE 1. Cont.

Compd. No.	M.P.ºC solvent of cryst.	Yield %	Molecular formula (Mol. wt.)	Analysis			Calcd/found%		
				C	H	N	S	Cl	Br
8b	215-216 EtOH	80	$C_{19}H_{16}SN_3Br$ (398)	57.28 57.3	4.02 4.0	10.55 10.6	8.04 8.1		20.100 20.1
9a	235-236 EtOH+AcOH	63	$C_{19}H_{15}OSN_2Cl$ (354.5)	64.31 64.3	4.23 4.2	7.89 7.9	9.02 9.1	10.01 10.1	
9b	284-249 EtOH+AcOH	70	$C_{19}H_{15}OSN_2Br$ (399)	57.14 57.1	3.76 3.8	7.01 7.1	8.02 8.0		20.05 20.1
10a	284-285 B	81	$C_{26}H_{19}OSN_2Cl$ (442.5)	70.50 70.5	4.29 4.3	6.32 6.3	7.23 7.2	8.02 8.1	
10b	291-292 B	79	$C_{26}H_{18}OSN_2Cl_2$ (447)	65.40 65.4	3.77 3.8	5.87 5.9	6.70 6.7	14.88 14.9	
10c	188-184 B+P.E.	84	$C_{26}H_{19}OSN_2Br$ (487)	64.06 64.1	3.90 3.9	5.74 5.8	6.57 6.6		16.42 16.4
10d	213-214 B	75	$C_{26}H_{18}OSN_2ClBr$ (521.5)	59.82 59.8	3.45 3.5	5.36 5.4	6.13 6.1	6.80 6.8	15.34 15.3
11a	286-287 B	60	$C_{26}H_{20}OSN_3Cl$ (457.5)	68.19 68.2	4.37 4.4	9.18 9.2	6.99 7.0	7.75 7.8	
11b	291-292 D	52	$C_{26}H_{19}OSN_3ClBr$ (536.5)	58.15 58.2	3.54 3.5	7.82 7.8	5.96 6.0	6.61 6.6	14.91 14.9
12	234-235 B+P.E.	50	$C_{29}H_{26}O_2SN_3Cl$ (515.5)	67.50 67.5	5.04 5.1	8.14 8.1	6.20 6.2	6.88 6.9	

where : B= benzene; P.E. = petroleum ether b.p. 80-120º; AcOEt= ethyl acetate and D = dioxane.

Reaction of 4,6-diaryl -1,2,3,4-tetrahydropyrimidine-2-thiones 2a, 2b with 2-chloroethylmethylether :Formation of 2,4-diaryl-6-(2-methoxyethyl)sulphanyl-1,2-dihydropyrimidine (7a,7b)

A mixture of compound 2*a* and/or 2*b* (0.01 mol), 2-chloroethyl methyl ether (0.01 mol) in ethanol (50 ml) containing sodium hydroxide (0.0125 mol) was stirred at 60ºC for 6hr. It was then poured into water (100 mL) and the precipitate that separated was collected washed well with water and dilute alcohol then recrystallized from ethanol to give 7*a*,7*b*, respectively (Table 1).

Reaction of 2a,b with acrylonitrile: Formation of 3-[4-(4-substituted-phenyl)-2-phenyl-6-sulphanyl-1,2-dihydro-1-pyrimidine]propanenitrile (8a,8b)

A mixture of compound 2*a* or 2*b* (0.01mol) and acrylonitrile (0.06 mol, 3ml) in 50mL of pyridine was refluxed for 6hr. It was cooled, poured into ice-dilute HCl and the product was filtered off, washed well with water and recrystallized from ethanol to give 8*a, b* (Table 1).

Reaction of 3a,b with AcOH-HCl mixture. Formation of 6,8-diaryl-3,4-dihydro-2H,6H-pyrimido[2,1-b][1,3]-thiazin-2-ones (9a,9b)

A suspension of compound 8*a* or 8*b* (0.01 mol) in glacial acetic acid-concentrated hydrochloric acid mixture (by volume) (30-10 ml) was refluxed for 4hr. The reaction mixture was concentrated (reduced pressure) and the semi-solid that separated was washed well with water then dried and triturated with light petroleum ether then recrystallized from ethanol acetic acid mixture to give compounds 9*a*,9*b* , respectively (Table 1).

Condensation of 9a,b with aromatic aldehydes: Formation of 3-(arylmethylene)-6,8-diaryl-3,4-dihydro-2H,6Hpyrimido[2,1-b][1,3]-thiazin-2-ones (10a-10d)

A mixture of compounds 9*a* or 9*b* (0.01mol), aromatic aldehydes namely, benzaldehyde and/or 2-chlorobenzaldehyde (0.01 mol) in glacial acetic acid-acetic anhydride mixture (25:15 ml) and freshly fused sodium acetate (0.05 mol) was heated on a steam bath under reflux for 3hr. After cooling, the reaction mixture was diluted with water and the product was filtered off, washed well with water then with dilute ethanol and recrystallized from the proper solvent to give 10*a*-10*d,* (Table 1).

Reaction of 5a,d with hydroxylamine hydrochloride: Formation of 3,6,8-triaryl-2,3-dihydro-4H,6H-isoxazolo[4,5-e]pyrimido[2,1-b]thiazine (11a,11b)

A mixture of compound 10*a* or 10*d* (0.01 mol), hydroxylamine hydrochloride (0.01 mol) in glacial acetic acid (20 ml) was refluxed for 6hr. After cooling it was poured into water and the solid that separated was collected, washed well with dilute alkali (Na_2CO_3) and recrystallized from benzene or dioxane to give 11*a*,11*b* (Table 1).

Reaction of 11a with 2-chloroethyl methyl ether: Formation of 3,6,8-triaryl-2-(2-methoxyethyl)-2,3-dihydro-4H,6H-isoxazolo[4,5-e]pyrimido[2,1-b] [1,3]thiazine (12)

To a suspension of 11*a* (0.01 mol) in dry DMF (25 ml) was added sodium hydride (0.4 g) in portions while stirring on a steam-bath (and the temperature was adjusted so not to exceed 65ºC for 1 hr, then 2-chloroethyl methyl ether was added, while stirring, and the reaction mixture was stirred for another 6hr at 40ºC. The excess solvent was evaporated (reduced pressure) and the semi-solid formed was triturated with light petroleum ether (b.p. 40-60º) and the product was recrystallized from benzene/pet-ether mixture (b.p. 40-60º) to give 12 (Table 1).

TABLE 2. Spectral data of the prepared compounds (2-12).

Compd. No.	IR spectra[a]	^{1}H-NMR spectra[b]	^{13}C-NMR spectra δ (75.5 MHz, DMSO-d_6)/or $CDCl_3$	Mass spectra m/z(%)
2a	3330 (υNH); 2982, 2890 (υCH); 2624 ((υSH), 1605 (υC=N)	10.9 (s, 1H, NH, D_2O exchangeable), 10.53 (d, 1H, NH), 3.14 (d, 1H, C_4-H), 4.23 (d, 1H, C_5-H), 6.79-8.01 (m, 9H, Ar–H).	130.3(CH), 134.8 (CH), 139.4 (C), 185.9 (CS), 186.7 (CCl).	303 M+2 (79.2) 301 M (48.8)
2b	3290 (υNH); 3005, 2990 (υCH); 2604 ((υSH), 1590 (υC=N).	10.91 (s, 1H, NH, exchangeable), 11.04 (d, 1H, NH exchangeable), 4.01 (d, 1H, C_4-H), 4.23 (d, 1H, C_5-H), 6.81-8.12 (m, 9H, Ar–H).	130.4(CH), 135.6 (CH), 140.6(C), 187.6 (CS), 189.8(CBr).	349 M+4 (13.7) 347 M+2 (62.1) 345 M (27.8)
3a	2992, 2880 (υCH); 1701, (υC=O); 1605 (υC=N)	3.45 (s, 2H, CH_2), 3.8 (d, 1H, C_5-H), 4.1 (d, C_6-H), 7.1-7.92 (m, 9H, Ar–H).	24.6(CH_2), 129.4 (CH), 131.2(CH), 137.4 (C), 162.6 (CO), 1606.8. (CS)	343 M+4 (43.9) 341 M (33.1)
3b	3005, 2992, 2829 (υCH); 1701, (υC=O); 1615 (υC=N).	4.01 (s, 2H, CH_2), 4.5 (d, 1H, C_5-H), 5.3 (d, C_6-H), 7.12-7.95 (m, 9H, Ar–H).	26.4(CH_2), 130 (CH), 131.2(CH), 137.4 (C), 165.4 (CO), 160.2 (CS)	389 M+4 (21.5) 387 M+2 (10.6) 385 M (29.8)
4a	2990, 2890 (υCH); 1705 (υC=O).	4.56 (d, 1H, C_5–H), 5.63 (d, 1H, C_6H), 7.2-7.96 (m 13H, Ar-H an aryl–CH).	124.3 (C), 126 (CH), 129.6 (CH), 130.4 (CH), 132.5 (CH)133.9 (CH), 134.3(CH), 137.4(C), 141.5 (C), 161.2(CO), 165.4(CO),169.6(CS)	421 M+2 (19.3) 419 M] (81.1)

TABLE 2. Cont.

Compd. No.	IR spectra[a]	^{1}H-NMR spectra[b]	^{13}C-NMR spectra δ (75.5 MHz, DMSO-d_6)/or $CDCl_3$	Mass spectra m/z(%)
4b	2992, 2888 (υCH); 1699, (υC=O).	4.62 (d, 1H, C_5–H), 5.61 (d, 1H, C_6-H), 7.21 – 7.95 (m, 13H, Ar–H and aryl-CH).		437 M+2 (28.3) 43 M (87.0)
4c	3005, 2990, (υCH); 1695 (υC=O).	4.57 (d, 1H, C_5-H), 5.67 (d, 1H, C_6-H), 7.21- 7.95 (m, 13H, Ar–H and aryl –CH).		467 M+4 (16.7) 465 M +2 (46.3) 463 M (34.3)
4d	2990, 2890 (υC-H); 1700, (υC=O).	4.61 (d, 1H, C_5–H), 5.66 (d, 1H, C_6-H), 7.3 – 7.95 (m, 13H, Ar–H and aryl -CH).		478 M+4 (15.3) 476 M+2 (71.6) 474 M (35.4)
4e	2992, 2890 (υCH); 1705, (υC=O), 1615 (υC=N).	4.59 (d, 1H, C_5–H), 5.57 (d, 1H, C_6-H), 7.23 – 7.98 (m, 14H, Ar–H and aryl-CH).		
4f	3005, 2990, (υCH); 1695 (υC=O).	4.62 (d, 1H, C_5–H), 5.59 (d, 1H, C_6-H), 7.29 – 7.95 (m, 15H, Ar–H and aryl-CH).		
5a	3150(cyclic NH); 3005, 2990 (υCH).	10.95 (d, 1H, cyclic NH, D_2O exchangeable) 4.93 (d, 1H, C_5-H), 5.8 (d, 1H, C_6-H), 5.43 (d, 1H, C_5-H 7.31-7.95 (m, 12H Ar-H).	119.6(C), 121.9 (C), 123.4 (C), 125.7 (CH), 127.9(CH), 128.4 (CH), 130.1 (CH), 132.9(CH), 134.3 (CH), 135.7 (CH), 167.1(CO), 169.4 (CS), 181.2 (CCl).	

TABLE 2. Cont.

Compd. No.	IR spectra[a]	^{1}H-NMR spectra[b]	^{13}C-NMR spectra δ (75.5 MHz, DMSO-d_6)/ or $CDCl_3$	Mass spectra m/z(%)
5b	3235(cyclic NH); 2992, 2888 (υCH).	10.92 (d, 1H, cyclic NH, D_2O exchangeable), 4.79 (d, 1H, C_9-H), 5.41 (d, 1H, C_5-H) 5.79(d, 1H, C_6-H), 7.23-7.89 (m, 12H Ar-H).		
6	2995, 2882, 2820 (υCH).	2.10 (s, 3H, O–CH_3), 2.71 (d, 2H, CH_2–CH_2), 3.1 (t, 2H, CH_2CH_2O), 4.71 (d, 1H, C_9-H), 5.13 (d, 1H, C_4-H), 5.69 (d, 1H, C_5-H), 7.29-7.91 (m, 12H, Ar-H).	17.3(CH_3), 19.9 (CH_2), 22.5 (CH_2O), 124.3 (C), 126.7 (C), 129.6(CH), 130.4 (CH), 132.5(CH), 133.9 (CH), 136.2 (C), 137.4 (C), 138 (CH), 141.5 (C), 162.7(CO), 168.9(CS)	552M $^{+\cdot}$ (19.6) 537M–CH_3 $^{+\cdot}$ (38.9) 508M–OCH_2 $^{+\cdot}$ (76.1)
7a	3225(υNH) 3005; 2992, 2828 (υCH).	10.91 (d, 1H, NH, D_2O exchangeable), 2.69 (t, 2H, CH_2,CH_2), 3.12(t, 2H, CH_2O), 3.41, (s, 3H, OCH_3), 4.79 (d, 1H, C_4-H), 5.69 (m, 1H, C_5-H), 7.45-8.01 (m, 9H, Ar-H).	26.4(SCH_2), 33.1 (CH_2O), 79.9 (OCH_3), 118.7 (CH), 129.4 (C), 129.6 (CH), 130.4 (CH), 131.2 (C), 132.8(CH), 133.9 (CH), 136.2 (C), 137.4 (C), 169.8 (CS)	
7b	3350(υNH); 3005, 2990, 2881, 2829 (υCH); 1605 (υC=N).	11.01 (d, 1H, NH, D_2O exchangeable), 2.91 (t, 2H, CH_2,CH_2), 3.14(t, 2H, CH_2O), 3.44, (S, 3H, OCH_3), 4.95 (d, 1H, C_4-H), 5.71 (m, 1H, C_5-H), 7.39-7.99 (m, 9H, Ar-H).	27.8(CH_2), 29.8 (CH_2), 116.8(CN), 129.4 (C), 131.2 (C), 137.4 (CH), 138.8 (C), 171.5(CS),	407 M+4 $^{+\cdot}$ (19.1) 405 M+2 $^{+\cdot}$ (77.6) 403 M $^{+\cdot}$ (28.4)

TABLE 2. Cont.

Compd. No.	IR spectra[a]	^{1}H-NMR spectra[b]	^{13}C-NMR spectra δ (75.5 MHz, DMSO-d_6)/ or $CDCl_3$	Mass spectra m/z(%)
8a	2223(υC–N), 2992, 2828 (υCH), 2607 (υSH) 1595 (υC=N).	8.1 (s, 1H, SH, D_2O exchangeable), 2.89 (t, 2H, $\underline{CH_2}$,CN), 3.7(t, 2H, $\underline{CH_2}$ CH_2), 4.94, (d, 1H, C_6-H), 5.01 (d, 1H, C_5-H), 7.1-7.9 (m, 9H, Ar-H).	22.4(CH_2), 27.3 (CH_2), 116.1(CN), 131.1 (C), 134.5 (CH), 136.7 (CH), 171.1(CSH).	356 M+1 (39.3) 354 M (15.4) 313 M-CH_3CN (100)
8b	2221(υC–N), 3001, 2991, 2882, 2820 (υCH), 2627 (υSH), 1601 (υC=N).	8.29 (s, 1H, SH, D_2O exchangeable), 2.91 (t, 2H, $\underline{CH_2}$,CN), 3.7(t, 2H, 2H, $\underline{CH_2}$ CH_2), 5.1 (d, 1H, C_6-H), 5.31 (d, 1H, C_5-H), 7.3-7.95 (m, 9H, Ar-H).		
9a	2929, 2882, 2828 (υCH), 1699 (υC=O).	2.59 (t, 2H, CH_2-CH_2), 3.01(t, 2H, 2H, CH_2 CO), 4.95 (d, 1H, C_6-H), 5.41 (d, 1H, C_7-H), 7.12-7.81 (m, 9H, Ar-H).	26.7(CH_2), 27.1 (CH_2), 116.8(CN), 129.4 (C), 166.9 (CO), 169.8 (CS).	356 M+2 (60.9) 342 M-CH (100)
9b	3005, 2999, 2821 (υCH), 1701 (υC=O).	2.61 (t, 2H, CH_2-CH_2), 3.11(t, 2H, CH_2CO), 5.01 (d, 1H, C_6-H), 5.65 (d, 1H, C_7-H), 7.21-7.83 (m, 9H, Ar-H).		
10a	2990, 2882, 2820 (υCH), 1690 (υC=O).	3.21 (S, 2H, CH_2), 4.91 (d, 1H, C_6-H), 5.3 (d, 1H, C_7-H), 7.19-8.01 (m, 15H, Ar-H) and 1H, Ar-CH=C).	27.4(CH_2), 114.3 (CN), 129.6(CH), 131.4 (CH), 132.9 (CH), 134.4 (C), 136.9(C), 137.4 (C), 161.2(CO), 169.8 (CS).	445 M+1 (19.2) 443 M (22.4)

TABLE 2. Cont.

Compd. No.	IR spectra[a]	^{1}H-NMR spectra[b]	^{13}C-NMR spectra δ (75.5 MHz, DMSO-d_6)/ or $CDCl_3$	Mass spectra m/z(%)
10b	2992, 2822 (υCH), 1699 (υC=O).	3.31 (S, 2H, CH_2), 4.95 (d, 1H, C_6-H), 5.81 (d, 1H, C_7-H), 7.19-8.12 (m, 14H, Ar-H and 1H, Ar-CH=C).		
10c	2992, 2820 (υCH), 1690 (υC=O).	3.47 (S, 2H, CH_2), 5.12 (d, 1H, C_6-H), 5.95 (d, 1H, C_7-H), 7.25-8.12 (m, 14H, Ar-H and 1H, Ar-CH=C).		
11a	3330 (υNH), 3005, 2990, 2828 (υCH) and devoid of (υC=O).	10.9 (d, 1H, NH, D_2O exchangeable), 3.1 (s, 2H, CH_2), 4.43 (d, 1H, C_3-H), 5.01 (d, 1H, C_7-H), 7.12-7.89 (m, 14H, Ar-H).	120.2(C), 122.1(C), 123.9 (C), 125.7 (CH), 127.9 (CH), 129.1 (CH), 131.4 (CH), 133.2 (CH), 135.3 (CH), 135.9 (CH), 168.1 (CO), 169.2 (CS).	459 M+1 (18.7) 457 M (10.1)
11b	3350 (υNH), 2999, 2882, 2820 (υCH) and devoid of (υC=O).	11.01 (d, 1H, NH, D_2O exchangeable), 2.54 (s, 2H, CH_2), 4.7 (d, 1H, C_3-H), 5.11 (d, 1H, C_6-H), 6.06 (d, 1H, C_7-H), 7.16-7.95 (m, 13H, Ar-H).		
12	Devoid of (υNH), 2990, 2828 (υC–H); 1601 (υC=N), 1180 (υC–O–N).	CH_2-O), 3.41 (s, 3H, 5.95 (d, 1H, C_7-H),	18.4 (CH2), 20.1 (CH_2), 23.3 (CH_2O), 125.7 (C), 127.6 (C), 129.7 (CH), 131.3 (CH), 132.9 (CH), 134.9 (CH), 137.1 (C), 138.4 (CH), 141.5 (C), 163.6 (CO), 169.2 (CS).	517 M+1 (17.3) 516 M (38.4)

Where a), υ in cm^{-1} ; b) δ in ppm

Results and Discussion

4, 6-Diaryl -1, 2- dihydropyrimidine-2(1*H*)-thione (1)[11] is used as a key starting compound in the synthesis of fused pyrimidine derivatives. Thus, compounds 1*a*, 1*b* reacted with zinc dust in the presence of glacial acetic acid to give the corresponding 4, 6-diaryl-1, 2, 3, 4-tetrahydropyrimidine-2-thiones 2*a*, 2*b*. The spectral data of compounds 2 agreed well with the proposed structure. The IR spectra of compounds 2 revealed the absorption bands of υ NH, C=N and υ S–H; the MS showed the characteristic fragmentation pattern due to the presence of chlorine atom (Table 2).

As a point of interest, compounds 2*a*, *2b* reacted with chloroacetic acid in glacial acetic acid acetic anhydride mixture (in adjusted temperature between (40-70ºC) in the presence of anhydrous sodium acetate to yield the corresponding 5, 7-diaryl-2, 3-dihydro-5*H*-thiazolo[3,2-*a*] pyrimidin-3-ones 3*a*,3*b*, respectively. The IR spectra of 3*a*, 3*b* revealed the presence of υ C=O, C=N and the absence of υNH (Table 2).

The reaction was believed to proceed via nucleophilic displacement by the sulfur nucleophile of the lactim form to the partially positive saturated carbon of the ethyl chloroacetate ester (S_N2), followed by internal cyclization.

Condensation of 3*a*, 3*b* with aromatic aldehydes, namely furfural, thiophene-2-aldehyde, isonicotinaldehyde or benzaldehyde in the presence of CH_3COONa and glacial acetic acid-acetic anhydride mixture afforded the corresponding 5, 7-diaryl-2-(arylmethylene)-2, 3-dihydro-5*H*-thiazolo [3,2-*a*] pyrimidin-3-ones (4*a-f).* The reaction of 4*a*,4*d* with hydroxylamine hydrochloride in refluxing glacial acetic acid containing anhydrous sodium acetate yielded the corresponding3,6,8-triaryl-2,3-dihydro-8*H*-isoxazolo [5`,4`:4,5] thiazolo [3,2-*a*] pyrimidines (5*a*,5*b).* Alkylation of compound 5*b*, with 2-chloroethylmethylether gave 6-(4-bromophenyl)-2- (2-methoxyethyl)- 8-phenyl-3- (2-thienyl) -2,3-dihydro-8*H*-isoxazolo [5`,4`:4,5] thiazolo[2,3-*a*]pyrimidine (6 *a*).

The structure of 6 was supported by the mass spectrum which revealed a molecular formula ($C_{26}H_{22}O_2S_2N_3Br$) (M^+=552). The ^{1}H-NMR spectrum showed one single each at δ 3.34 ppm and δ 3.31 ppm for the two CH–N–cyclic protons, a signal band at δ2.1 ppm to the three protons of CH_3 and two doublets near δ3.41 and 3.45 ppm for the CH—CH protons, and a multiplet at δ 7.12-8.12 ppm for the 12 aromatic protons (Table 2).

As a point of interest, alkylation of compound 2*b* with 2-chloroethyl methyl ether in alcoholic sodium hydroxide afforded the corresponding 2, 4-diaryl-6-(2-methoxyethyl)sulphanyl-1,2-dihydropyrimidine 7.The IR spectrum of compound 7 revealed the presence of υ NH, υ C=N and devoid of υ SH (Table 2). The ^{1}H-NMR spectrums revealed signals for the methyl ethyl ether protons, the CH–CH protons, the 10 aromatic protons and the NH proton (Table 2). In a similar manner, cyanoethylation of compounds 2*a*, 2b with an equimolecular amount of

acrylonitrile in pyridine gave 3-[4-(4-substituted-phenyl)-2-phenyl-6-sulphanyl-1, 2-dihydro-1-pyrimidine]propanenitrile (8*a* ,8*b)* . Due to the ambient nature of the pyrimidine-2(1*H*)thione derivatives 2*a*,2*b* either the thione [A] or thiol [B] are possible[17] . The ^{13}C-NMR spectrum of 2*a*,2*b* gave signal at δ 185.9 and 187.6 assignable to thiocarbonyl carbon at C-2 which explains the nucleophilic attack of the pyrimidine ring system to the methyl carbon of the nitrile. The carbon peak due to the thiol form was clearly observed for compounds 8*a*, 8*b* around δ 170 (Table 2). The IR spectra of 8*a*, 8*b* revealed the presence of the υ SH, C≡N and C=N (Table 2).

Treatment of compounds 3*a*, 3*b* with glacial acetic acid conc. HCl mixture affected cyclization to the corresponding 6,8-diaryl-3,4-dihydro-2*H*,6*H*-pyrimido[2,1-*b*][1,3]-thiazin-2-ones 9*a*,9*b*, this is in agreement with the previous findings of Aly, *et al*.[18], respectively. This was confirmed by elemental analysis (Table 1) and spectral data (Table 2).

Moreover, condensation of 9*a*,9*b* with aromatic aldehydes namely benzaldehyde and/or 2-chloro-benzaldehyde afforded the corresponding 3-(arylmethylene)- 6,8-diaryl-3,4-dihydro-2*H*,6*H*-pyrimido [2,1-*b*] [1,3]-thiazin-2-ones 10*a*-10*d* , the structures of which were in agreement with their spectral data (Table 2). Compounds 10*a or* 10*d* were subjected to further ring formation. Thus, the reaction of 10*a or* 10*d* with hydroxylamine hydrochloride in boiling glacial acetic acid in the presence of anhydrous sodium acetate yielded 3,6,8-triaryl-2,3-dihydro-4*H*,6*H*-isoxazolo [4,5-*e*] pyrimido[2,1-*b*] thiazine (11*a*,11*b*), respectively. The structure of 11*a* was supported by its MS which revealed a molecular formula $C_{26}H_{20}O\ SN_3Cl$ (M^+ = 457) and ^{1}H-NMR spectrum which induced one single band δ 2.54 ppm (2H), assigned to the CH_2 protons, doublet band near δ 3.41 ppm for the CH protons, doublet band near δ 10.99 ppm for the NH proton (exchangeable with D_2O) and a multiplet at δ 7.12-7.89 ppm for the 14 aromatic protons (Table 2).

Alkylation of compound 11*a* with 2-chloroethyl methyl ether afforded 3,6,8-triaryl-2-(2-methoxyethyl)-2,3-dihydro-4*H*, 6*H*-isoxazolo[4,5-*e*]pyrimido [2,1-*b*] [1,3] thiazine (12). The IR spectra of compound 12 revealed the presence of υ C=N, C—O—N (isoxazolo), agreed well with the proposed structure (Table 2).

Antimicrobial activity

The *in vitro* antimicrobial activity of the new derivatives 2-6, 8 and 11 against several pathogens representatives namely, *Escherichia coli*, *Bacillus subtilis*, *Mycobacterium philei*, *Staphylococcus aureus*, *Aspergillus niger* and *Candida albicans*. The disk diffusion method[19,20] was used. Whatman No.1 filter paper disks were sterilized by autoclaving for 1hr at 140ºC. The sterile disks were impregnated with the tested compounds (250 μg mL^{-1}). Agar plates were uniformly surface inoculated with fresh broth culture. The impregnated disks were placed on the medium suitably spaced apart and the plates were incubated at 5ºC for 1hr, to permit good diffusion and were then transferred to an

incubator at 28°C for 24hr. The zones of inhibition were measured. The results of antimicrobial activity tests are listed in MICs were recorded as the minimum concentration of a compound that inhibits the growth of tested microorganisms. All of the compounds tested illustrated significant antibacterial and antifungal activity when compared with reference drugs. The antibacterial assessment revealed that the compounds possess weak activities. The MIC values are generally within the range of 3.9-250 μg/ml against all evaluated strains.

TABLE 3. MIC values (μg/ml) of compounds 2-6, 8 and 11.

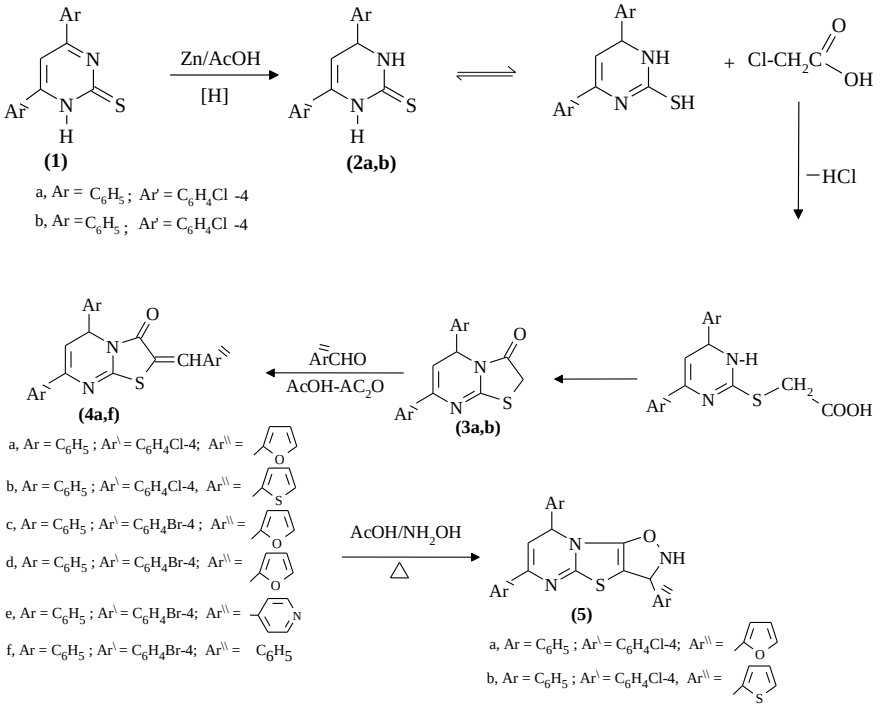
Compd. No.	A	B	C	D	E	F
2a	250	15.6	62.5	125	250	250
2b	250	125	31.25	125	125	125
3a	125	125	125	125	62.5	62.5
3b	125	62.5	62.5	62.5	62.5	125
4a	125	125	125	125	125	125
4b	250	125	42.5	125	250	250
4c	250	125	125	125	125	125
4d	250	250	125	250	125	125
4e	250	250	250	250	250	250
4f	125	31.25	125	31.25	62.5	62.5
5a	31.25	250	125	125	62.5	62.5
5b	125	31.25	125	125	62.5	62.5
6	125	125	125	125	62.5	125
8a	250	250	250	3.9	125	125
8b	250	250	250	62.5	31.25	62.5
11a	125	15.6	125	125	62.5	125
11b	125	125	125	125	125	125
Reference substance-1	15.60	15.60	31.25	31.25	31.25	250
Microorganism used		--	--	--	250	250

References substance -1: Chloramphenicol, Microorganism used; *A: Escherichia coli* (NRRL B-3704); B: *Bacillus subtiles* (NRRL B-3710); C: *Mycobacterium philei* (isolates obtained from Al-Azhar Uni. Fac. of Science); D: *Staphylococcus aureus* (NRRL B-767); E: *Aspergillus niger* (isolates obtained from Al-Azhar Uni. Fac. of Science); F: *Candida albicans* (isolates obtained from Al-Azhar Uni. Fac. of Science).

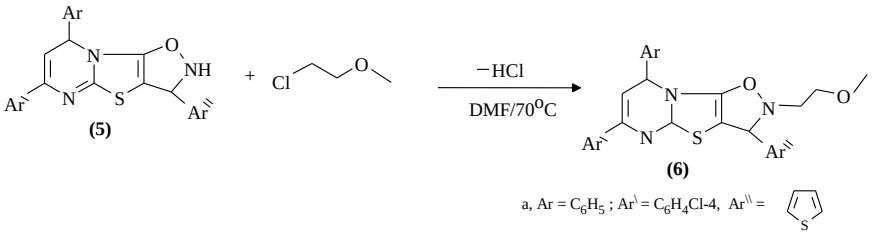
In comparing their MIC values with chloramphenicol, all compounds were effective against *S.aureus*. Compounds 3*b*, 4*f*, 8*b* and especially 8*a* showed very high activity. Compounds 2*a*, 3*b*, 4*f*, 5*b* and 11*a* have shown high activity against *E.coli*, while compounds 2*a*, 3*b*, 4*f*, 5*b* and especially 11*a* have shown

strong activity against *B.subtilis.* Compounds 2*a*, 2*b*, 3*b*, 4*b*, have shown the highest activity against *M. philei.*

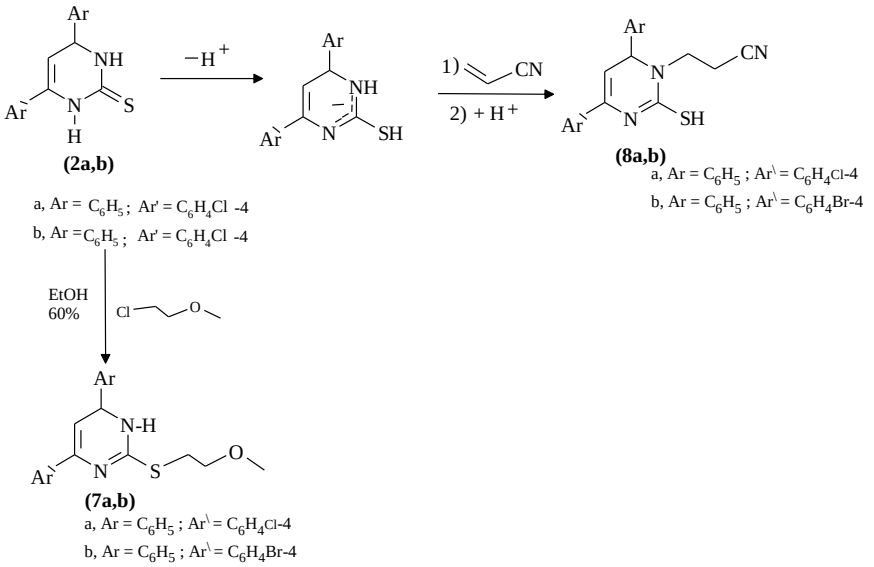
The antifungal activity of the compounds was studied with two pathogenic fungi. Flucanazole has been used as a reference for inhibitory activity against fungi. All compounds showed good antifungal activity. When compared flucanazole, thirteen compounds are more active (MIC (250µg/ml), and three compounds are equipotent (250µg/ml) against *A. niger* and *C.albicans.*



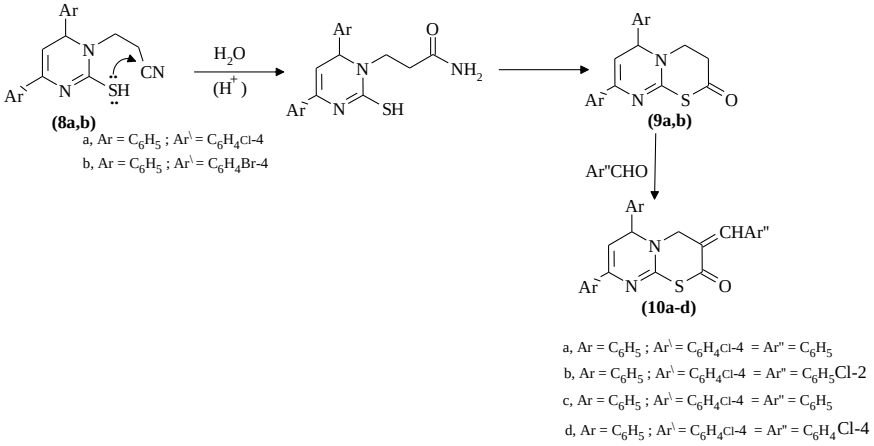
Scheme 1.



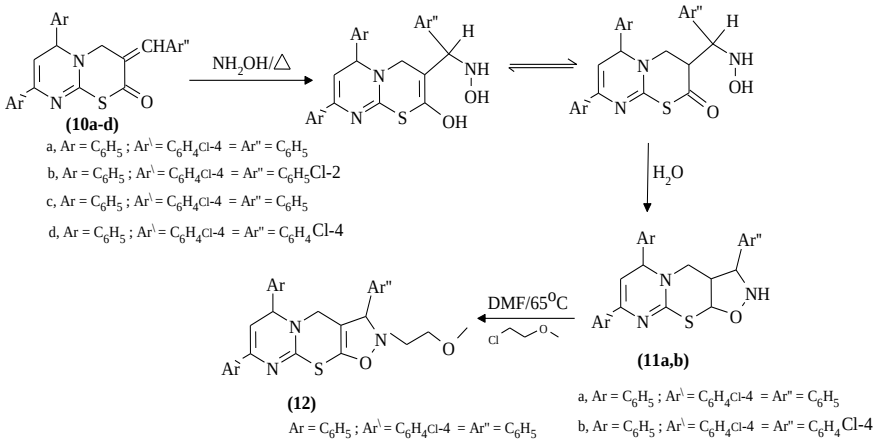
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

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سلوك الثيوبريميدينات تجاه بعض الكواشف الإلكتروفيلية والنيوكلوفيلية

ناهد فتح الله عبد الغفار ، فكرية محمد احمد سليمان و نادية طه علي داوود
قسم الكيمياء – كلية العلوم (بنات) – جامعة الأزهر – القاهرة – مصر .

تم تحضير مشتقات ايزواكسازولوثيازولو بيريميدين (5,6) و تحضير مركبات 4,6- ثنائي اريل (H)-2-بيريميدين -2- ثيون (1a,b) وكذلك ايزواكسازولو ثيازينو بيريميدين (11,12) وذلك بتفاعل (1a,b) مع بعض الكواشف الإلكتروفيلية والنيوكلوفيلية . تم دراسة التأثير الحيوي لبعض المركبات التي تم تحضيرها تجاه الميكروبات.