Def Sci J, Vol 31, No 1, January 1981, pp 15–22

Studies in Heterocyclic Compounds—Part XXXIII : Synthesis and *in vitro* screening of some 1,3-diaryl-5-(arylazo/N-substituted *p*-sulphamylbenzeneazo)dihydro-2-thioxo-4,6(1*H*, 5*H*)-pyrimidinediones

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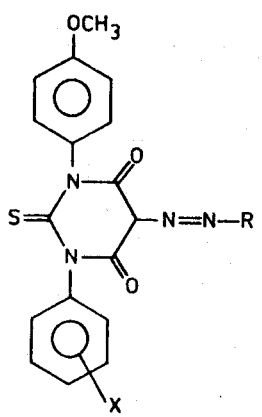
Received 3 September 1979

Abstract. 1-Phenyl-3-(*p*-methoxyphenyl)- and 1,3-di(*p*-methoxyphenyl)dihydro-2-thioxo-4,6 (1*H*, 5*H*)-pyrimidinediones have been synthesised and coupled with different diazotised simple and sulphonamide bases to furnish the corresponding 5-(arylazo/N-substituted *p*-sulphamylbenzeneazo)dihydro-2-thioxo-4,6(1*H*, 5*H*)-pyrimidinediones. On *in vitro* screening these were found to exhibit considerable activity against a number of micro-organisms.

Introduction

In view of the importance of dihydro-2-thioxo-4,6(1*H*, 5*H*)-pyrimidinediones in therapy and textile industry[1] and encouraged by the results obtained during the course of earlier work on the synthesis and screening of arylazo pyrimidinediones[2], it was thought of interest to synthesise some new pyrimidinedione congeners having the methoxyl group in one or both the phenyl rings attached at positions 1 and 3 of the pyrimidine nucleus since the presence of the methoxyl group has been reported to



a : X = *H*; *p*-OCH_3; R = C_6H_4R'
b : X = *H*; *p*-OCH_3; R = $C_6H_4SO_2NHR'$

Figure 1.

enhance the activity considerably in arylazo azoles[3]. This work would provide an opportunity to study the effect of replacement of halogen and alkyl groups by an alkoxyl on the antibacterial properties, their comparison with the earlier work, thus establishing the structure activity relationship.

The present paper describes the synthesis of 1-phenyl-3-(*p*-methoxyphenyl)- and 1,3-di(*p*-methoxyphenyl)dihydro-2-thioxo-4,6(1*H*, 5*H*)-pyrimidinediones and their coupling with diazotised simple and sulphonamide bases to yield 1-phenyl-3-(*p*-methoxyphenyl)- and 1,3-di(*p*-methoxyphenyl)-5-(arylazo/N-substituted *p*-sulphamylbenzeneazo)dihydro-2-thioxo-4,6(1*H*, 5*H*)-pyrimidinediones of the type as shown in Figure 1 (a, b). The homogeneity and purity of these compounds were checked by TLC and elemental analysis and structure assigned on the basis of IR and NMR spectral studies.

Experimental

Synthesis of 1-phenyl-3-(p-methoxyphenyl)dihydro-2-thioxo-4,6(1H, 5H)-pyrimidinediones

Acetyl chloride (15 ml) was added to a mixture of 1-phenyl-3-(*p*-methoxyphenyl)-thiourea (10.4g; 0.04 mol) and malonic acid (4.26g; 0.041 mol) contained in a R.B. flask (100 ml) and the contents refluxed on a water bath for 30 minutes. The reaction mixture on cooling and treating with water solidified to a yellow coloured mass which was broken and finally powdered in a mortar in presence of water. The heavy solid was filtered, washed first with water and then with hot ethanol; *pure 1-phenyl-3-(p-methoxyphenyl)dihydro-2-thioxo-4,6(1H, 5H)-pyrimidinedione* was crystallised from glacial acetic acid as a yellow solid, m.p. 173-4 °C. (Yield: 7.3g; 55.6%).

(Found: *C*, 62.1; *H*, 4.9. $C_{17}H_{16}N_2O_3S$ requires *C*, 62.2; *H*, 4.9%). IR ν_{max}^{KBR}: 1687, 1695 cm^{-1} (> *C* = *O*); 1031 cm^{-1} (> *C* = *S*); 1333 cm^{-1} (—*C*(=*S*)—*N*) and 813, 826 cm^{-1} (1,4-substituted phenyl).

NMR (TFA) : 3-*p*-OCH_3 (3.45δ, *S*, 3*H*); —$COCH_2CO$— (3.75δ, *S*, 2*H*) and aromatic protons (6.65-7.0δ, m, 9*H*).

1,3-Di(*p-methoxyphenyl)dihydro-2-thioxo*-4,6(1*H*, 5*H*)-*pyrimidinedione* was similarly prepared and crystallised from glacial acetic acid as a pale yellow solid, m.p. 202 °C. (Yield : 60.0%).

Found : *C*, 60.7; *H*, 4.4. $C_{18}H_{16}O_4N_2S$ requires *C*, 60.7; *H*, 4.5%). IR ν_{max}^{KBR}: 1701, 1724 cm^{-1} (> *C* = *O*); 1031 cm^{-1} (> *C* = *S*); 1333 cm^{-1} (—*C*(=*S*)—*N*) and 820 cm^{-1} (1, 4-substituted phenyl).

NMR ($CDCl_3$ + TFA) : 1 and 3-*p*-OCH_3 (3.9δ, *S*, 6*H*); —$COCH_2CO$—(4.2δ, *S*, 2*H*) and aromatic protons (7.15δ, unresolved singlet, 8*H*).

The NMR spectrum (DMSO) of 1-(*p*-methoxyphenyl)-3-phenyl- and 1,3-di-(*p*-methoxyphenyl)thioureas show a singlet due to *NH* protons at 10.70δ and 10.52δ respectively which is absent in the NMR spectra (DMSO) of the two pyrimidinediones thereby confirming its cyclic structure which is further supported by the absence of any band due to *NH* group in the region 3100-3300 cm^{-1} in the IR spectrum of these compounds.

Synthesis of 1-*phenyl*-3-(*p-methoxyphenyl*)-5-(*arylazo/N-substituted p-sulphamyl-benzeneazo*)*dihydro-2-thioxo*-4,6(1*H*, 5*H*)-*pyrimidinediones*

A diazotised solution of the base (0.0015 mol) was gradually added to a well cooled, mechanically stirred solution of 1-phenyl-3-(*p*-methoxyphenyl)dihydro-2-thioxo-4,6 (1*H*, 5*H*)-pyrimidinediones (0.0015 mol) in dioxane-ethanol mixture containing sodium acetate (2g). The reaction mixture was further stirred for 5 min. and the solid separated on addition of ice-cold water was filtered, dried and crystallised from DMF-ethanol mixture.

Similar set of reactions was carried out with 1,3-di(*p*-methoxyphenyl)dihydro-2-thioxo-4,6(1*H*, 5*H*)-pyrimidinediones and all the synthesised compounds have been recorded in Table 1-4.

The IR spectra of the synthesised azo compounds showed bands at 1689-1739 cm^{-1} (doublet) ($>C=O$), 1026-1031 cm^{-1} ($>C=S$), 1333 cm^{-1} ($-\underset{\underset{S}{\|}}{C}-N$), 1587-1600 cm^{-1} ($N = N$) and 813-833 cm^{-1} (1,4-substituted phenyl). In the case of 5-(N-substituted *p*-sulphamylbenzeneazo)derivatives bands at 1087 and 1266 cm^{-1} are characteristic of $S = O$ symmetric and unsymmetric vibrational modes, while bands at 3350-3400 cm^{-1} may be due to *NH* group.

The azo structure has also been confirmed by NMR spectral studies. In the case of 5-arylazo analogues, there is no hump or peak due to *NH* or *OH* protons. The *CH* protons of position 5 move downfield and merge with aromatic protons due to the presence of three electron attracting groups around it.

Different 1,3-diaryl-5-(arylazo/N-substituted *p*-sulphamylbenzeneazo)dihydro-2-thioxo-4,6(1*H*, 5*H*)-pyrimidinediones when subjected to *in vitro* screening at two different concentrations of 50 μg/ml and 100 μg/ml against *S. aureus*, *E. coli* and *P. pyocyanea* showed promising results.

The activity of the compounds synthesised by coupling 1-phenyl-3-(*p*-methoxyphenyl)-dihydro-2-thioxo-4,6(1*H*, 5*H*)-pyrimidinediones with simple and sulphonamide bases, against three micro-organism is in the order of *P. pyocyanea* > *S. aureus* > *E. coli*. It was further observed that the introduction of a methoxyl group in the phenyl ring attached at position-3 as in 1,3-di(*p*-methoxyphenyl)-analogues renders the compound less active against all the three micro-organisms which is in conformity with our earlier findings[4]; however, the sequence of order of activity against the three strains is the same.

It was further observed that the azo derivatives synthesised from sulphonamide bases were more active as compared to those prepared from simple bases against all the three micro-organisms.

Table 1. 1-Phenyl-3-(*p*-methoxyphenyl)-5-(arylazo)dihydro-2-thioxo-4,6(1*H*, 5*H*)-pyrimidinediones

(Fig. 1a : X = H; R = C_6H_4R')

S. No.	R′	M.P. (°C)	Colour	Yield (%)	Crystallisation solvent	Molecular formula	Percentage			
							Found		Requires	
							C	*H*	*C*	*H*
1	*H*	288	Y	74	DMF/EtOH	$C_{23}H_{18}N_4O_3S$	64.1	4.2	64.2	4.2
2	*o*-Methyl	282	O	71	DMF/EtOH	$C_{24}H_{20}N_4O_3S$	64.8	4.4	64.9	4.5
3	*m*-Methyl	252	O	69	DMF/EtOH	$C_{24}H_{20}N_4O_3S$	64.6	4.4	64.9	4.5
4	*p*-Methyl	289	R	72	DMF/EtOH	$C_{24}H_{20}N_4O_3S$	64.5	4.3	64.9	4.5
5	*o*-Chloro	292	O	76	DMF/EtOH	$C_{23}H_{17}N_4O_3SCl$	59.4	3.7	59.5	3.7
6	*m*-Chloro	233	B	75	DMF/EtOH	$C_{23}H_{17}N_4O_3SCl$	59.5	3.6	59.5	3.7
7	*p*-Chloro	275	R	79	DMF/EtOH	$C_{23}H_{17}N_4O_3SCl$	59.2	3.6	59.5	3 7
8	*o*-Bromo	274	O	79	DMF/EtOH	$C_{23}H_{17}N_4O_3SBr$	54.1	3.1	54.2	3.3
9	*p*-Bromo	231	B	80	DMF/EtOH	$C_{23}H_{17}N_4O_3SBr$	54.2	3.1	54.2	3.3
10	*o*-Nitro	267	B	78	DMF/EtOH	$C_{23}H_{17}N_5O_5S$	58.0	3.6	58.1	3.6
11	*m*-Nitro	239	B	80	DMF/EtOH	$C_{23}H_{17}N_5O_5S$	58.1	3.5	58.1	3.6
12	*p*-Nitro	171	B	79	DMF/EtOH	$C_{23}H_{17}N_5O_5S$	57.9	3.5	58.1	3.6
13	*o*-Methoxy	289	BY	74	DMF/EtOH	$C_{24}H_{20}N_4O_4S$	62.4	4.2	62.6	4.3
14	*m*-Methoxy	254	B	72	DMF/EtOH	$C_{24}H_{20}N_4O_4S$	62.1	4.3	62.6	4.3
15	*p*-Methoxy	132	Y	74	DMF/EtOH	$C_{24}H_{20}N_4O_4S$	62.5	4.3	62.6	4.3
16	2,5-Dichloro	287	B	80	DMF/EtOH	$C_{23}H_{16}N_4O_3SCl_2$	55.3	3.1	55.4	3.2

Table 2. 1-Phenyl-3-(*p*-methoxyphenyl)-5-(N-substituted *p*-sulphamylbenzeneazo)dihydro-2-thioxo-4,6(1*H*, 5*H*)-pyrimidinediones (Fig. 1b : X = *H*; R = $C_6H_4SO_2NHR'$)

S. No.	R′	M.P. (°C)	Colour	Yield (%)	Crystallisation solvent	Molecular formula	Percentage			
							Found		Requires	
							C	*H*	*C*	*H*
1	*H*	>300	BY	65	DMF/EtOH	$C_{23}H_{19}N_5O_5S_2$	54.1	3.7	54.2	3.7
2	Acetyl	282	B	67	DMF/EtOH	$C_{25}H_{21}N_5O_6S_2$	54.2	3.7	54.4	3.8
3	Phenyl	306	Y	66	DMF/EtOH	$C_{29}H_{23}N_5O_5S_2$	59.5	3.6	59.5	3.9
4	*o*-Methylphenyl	177	B	63	DMF/EtOH	$C_{30}H_{25}N_5O_5S_2$	60.0	4.2	60.1	4.2
5	*m*-Methylphenyl	296	B	63	DMF/EtOH	$C_{30}H_{25}N_5O_5S_2$	60.1	4.1	60.1	4.2
6	*p*-Methylphenyl	263	R	66	DMF/EtOH	$C_{30}H_{25}N_5O_5S_2$	60.1	4.0	60.1	4.2
7	*o*-Chlorophenyl	160	B	68	DMF/EtOH	$C_{29}H_{22}N_5O_5S_2Cl$	56.0	3.3	56.0	3.5
8	*p*-Bromophenyl	244	RB	73	DMF/EtOH	$C_{29}H_{22}N_5O_5S_2Br$	52 0	3.5	52.2	3.6
9	*o*-Methoxyphenyl	251	G	68	DMF/EtOH	$C_{30}H_{25}N_5O_6S_2$	58.1	4.0	58.0	4.1
10	*p*-Nitrophenyl	261	RB	70	DMF/EtOH	$C_{29}H_{22}N_6O_7S_2$	55.1	3.5	55.2	3.5
11	Guanidyl	276	B	66	DMF/EtOH	$C_{24}H_{21}N_7O_5S_2$	52.1	3.7	52.3	3.8
12	Pyrimidin-2-yl	205	BL	71	DMF/EtOH	$C_{27}H_{21}N_7O_5S_2$	55.1	3.6	55.2	3.6
13	2,6-Dimethyl-pyrimidin-4-yl	170	BL	67	DMF/EtOH	$C_{29}H_{25}N_7O_5S_2$	55.6	4.1	55.9	4.0
14	4,6-Dimethyl-pyrimidin-2-yl	115	BL	73	DMF/EtOH	$C_{29}H_{25}N_7O_5S_2$	55.9	4.0	55.9	4.0
15	4-Methyl-pyrimidin-2-yl	189	Y	72	DMF/EtOH	$C_{28}H_{23}N_7O_5S_2$	55.9	3.6	55.9	3.8
16	Thiazol-2-yl	182	B	70	DMF/EtOH	$C_{26}H_{19}N_6O_5S_3$	52.7	3.1	52.8	3.2
17	3-Methoxy-pyrizin-6-yl	186	B	69	DMF/EtOH	$C_{28}H_{23}N_7O_6S_2$	54.3	3.6	54.5	3.7
18	1-Phenyl-pyrazol-4-yl	245	B	68	DME/EtOH	$C_{32}H_{24}N_7O_5S_2$	59.0	3.7	59.1	3.7

Table 3. 1,3-*Bis*(*p*-methoxyphenyl)-5-(arylazo)dihydro-2-thioxo-4,6(1*H*, 5*H*)-pyrimidinediones (Fig. 1a : X = *p*-OCH_3 ; R = C_6H_4R')

S. No.	R′	M.P. (°C)	Colour	Yield (%)	Crystallisation solvent	Molecular formula	Percentage			
							Found		Requires	
							C	*H*	*C*	*H*
1	*H*	206	BL	75	GAA/EtOH	$C_{24}H_{20}O_4N_4S$	62.5	4.3	62.6	4.3
2	*o*-Methyl	197	Grey	73	GAA/EtOH	$C_{25}H_{22}O_4N_4S$	63.1	4.5	63.3	4.6
3	*m*-Methyl	183	B	68	GAA/EtOH	$C_{25}H_{22}O_4N_4S$	63.2	4.5	63.3	4.6
4	*p*-Methyl	192	B	72	GAA/EtOH	$C_{25}H_{22}O_4N_4S$	63.1	4.4	63.3	4.6
5	*o*-Chloro	294	B	77	DMF/EtOH	$C_{24}H_{19}O_4N_4SCl$	58.3	3.8	58.4	3.9
6	*m*-Chloro	212	BL	76	DMF/EtOH	$C_{24}H_{19}O_4N_4SCl$	58.2	3.7	58.4	3.9
7	*p*-Chloro	205	B	80	GAA/EtOH	$C_{24}H_{19}O_4N_4SCl$	58.3	3.7	58.4	3.9
8	*o*-Bromo	300	B	79	DMF/EtOH	$C_{24}H_{19}O_4N_4SBr$	53.2	3.3	53.4	3.5
9	*p*-Bromo	211	BL	81	DMF/EtOH	$C_{24}H_{19}O_4N_4SBr$	53.2	3.2	53.4	3.5
10	*o*-Nitro	198	BL	79	GAA/EtOH	$C_{21}H_{19}O_6N_5S$	56.9	3.7	57.0	3.8
11	*m*-Nitro	186	B	81	GAA/EtOH	$C_{24}H_{19}O_6N_5S$	56.7	3.7	57.0	3.8
12	*p*-Nitro	196	BL	80	GAA/EtOH	$C_{21}H_{19}O_6N_5S$	56.8	3.6	57.0	3.8
13	*o*-Methoxy	199	BL	75	GAA/EtOH	$C_{25}H_{22}O_5N_4S$	61.1	4.4	61.2	4.5
14	*m*-Methoxy	190	BL	73	GAA/EtOH	$C_{25}H_{22}O_5N_4S$	61.2	4.3	61.2	4.5
15	2,5-Dichloro	289	BL	81	DMF/EtOH	$C_{24}H_{18}O_4N_4SCl_2$	54.3	3.3	54.5	3.4

Table 4. 1,3-*Bis*(*p*-methoxyphenyl)-5-(N-substituted *p*-sulphamylbenzeneazo)dihydro-2-thioxo-4,6(1*H*, 5*H*)-pyrimidinediones (Fig. 1b : X = *p*-OCH_3; R = $C_6H_4SO_2NHR'$)

S. No.	R′	M.P. (°C)	Colour	Yield (%)	Crystallisation solvent	Molecular formula	Percentage			
							Found		Requires	
							C	*H*	*C*	*H*
1	*H*	185	BL	68	GAA/EtOH	$C_{24}H_{21}O_6N_5S_2$	53.3	3.8	53.4	3.9
2	Acetyl	171	BL	69	DMF/EtOH	$C_{26}H_{23}O_7N_5S_2$	53.6	4.0	53.7	4.0
3	Phenyl	265	B	65	GAA/EtOH	$C_{30}H_{25}O_6N_5S_2$	58.4	4.0	58.5	4.1
4	*o*-Methylphenyl	184	B	65	GAA/EtOH	$C_{31}H_{27}O_6N_5S_2$	59.0	4.2	59.1	4.3
5	*m*-Methylphenyl	215	BL	63	DMF/EtOH	$C_{31}H_{27}O_6N_5S_2$	59.1	4.2	59.1	4.3
6	*p*-Methylphenyl	272	O	68	GAA/EtOH	$C_{31}H_{27}O_6N_5S_2$	59.0	4.1	59.1	4.3
7	*o*-Chlorophenyl	244	B	69	DMF/EtOH	$C_{30}H_{24}O_6N_5S_2Cl$	55.8	3.6	55.9	3.7
8	*m*-Chlorophenyl	259	R	67	DMF/EtOH	$C_{30}H_{24}O_6N_5S_2Cl$	55.7	3.5	55.9	3.7
9	*o*-Methoxyphenyl	241	O	67	GAA/EtOH	$C_{31}H_{27}O_7N_5S_2$	57.4	4.2	57.7	4.2
10	*p*-Nitrophenyl	205	B	71	GAA/EtOH	$C_{30}H_{24}O_8N_6S_2$	54.3	3.3	54.5	3.6
11	Guanidyl	>300	O	68	DMF/EtOH	$C_{25}H_{23}O_6N_7S$	51.5	4.0	51.6	4.0
12	Pyrimidin-2-yl	182	B	72	GAA/EtOH	$C_{28}H_{23}O_6N_7S$	54.3	3.5	54.4	3.7
13	2,6-Dimethyl pyrimidin-4-yl	216	BO	69	GAA/EtOH	$C_{30}H_{27}O_6N_7S$	55.7	4.0	55.8	4.2
14	4,6-Dimethyl pyrimidin-2-yl	194	B	74	GAA/EtOH	$C_{30}H_{27}O_6N_7S$	55.6	4.1	55.8	4.2
15	2,6-Dimethoxy pyrimidin-4-yl	228	O	71	GAA/EtOH	$C_{30}H_{27}O_8N_7S$	53.1	4.0	53.2	4.0
16	4-Methyl pyrimidin-2-yl	204	O	72	GAA/EtOH	$C_{29}H_{25}O_6N_7S$	55.0	3.8	55.1	4.0
17	3-Methoxy pyrazin-6-yl	274	Y	67	GAA/EtOH	$C_{29}H_{25}O_7N_7S_2$	54.3	3.8	54.6	3.9
18	1-Phenyl pyrazol-4-yl	169	B	69	GAA/EtOH	$C_{33}H_{27}O_6N_7S_2$	58.0	3.9	58.1	4.0
19	Thiazol-2-yl	214	B	72	DMF/EtOH	$C_{27}H_{22}O_6N_6S_3$	55.7	5.2	55.9	5.3
20	5-Methyl-1,3,4-thiadiazol-2-yl	>300	O	74	DMF/EtOH	$C_{27}H_{24}O_6N_7S_3$	50.5	3.7	50.8	3.8

GAA = Glacial acetic acid; DMF = Dimethylformamide
B = Brown; BL = Black; O = Orange; Y = Yellow

When these results are compared with those reported earlier[5] it was found that replacement of methyl by a methoxyl group in one of the phenyl rings of the pyrimidinediones decreases the activity.

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