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Heterocyclic compounds - Part-1 : Preparation of some s-triazine derivatives as potential antimicrobial agents

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ABSTRACT

Formation of compounds, s-triazine derivatives **(6a-z, 8a-i)** and **(9)** have been reported from 6-p-anisyl-5-cyano-2-hydrazino-3-N-methyl-3, 4-dihydropyrimidin-4-one **(3)**. The compounds were evaluated *in vitro* for antimicrobial activity against several microbes.

KEYWORDS

2-Mercapto pyrimidine;
2-Methylthiopyrimidine;
2-Hydrazinopyrimidine;
s-Triazine derivatives.

INTRODUCTION

The s-triazine moiety plays vital role in heterocyclic chemistry largely due to the wide ranging biological activity such as antimalerial[1], anticancer[2], antiulcer[3], local anaesthetic[4], anticonvulsant[5] and muscle relaxant[6], antimicrobial[7], Jensch claimed that s-triazine derivatives are effective in diseases due to bacteria and protozoa[8]. These valied findings stimulated us to prepare s-triazine derivatives bearing pyrimidine moiety.

The starting compound 6-p-anisyl-5-cyano-2-mercapto-3,4-dihydropyrimidin-4-one **(1)** was prepared by reported method[9], compound **(1)** was alkylated with methyl iodide to obtained **(2)** which on treatment with hydrazine produced **(3)**. Condensation of **(3)** with cyanuric chloride furnished compound **(4)**. Reaction of **(4)** with different alkyl/aryl amines at 35^{0}C temperature yielded 6-p-anisyl-5-cyano-3-N-methyl-2-(2'-alkyl/aryl amino-4'chloro-s-triazin-6'-yl hydrazino)-3, 4-dihydropyrimidin-4-one **(5)**, further condensation of **(5)** with different alkyl/aryl amines at 110^{0}C temperature afforded corresponding 6-p-anisyl-5-cyano-3-N-methyl-2-(2'-alkyl/aryl amino-4'-alkyl/aryl amino-s-triazin-6'-yl hydrazino)-3,4-dihydropyrimidin-4-ones **(6a-z)**.

6-p-Anisyl-5-cyano-2-hydrazino-3-N-methyl-3,4-dihydropyrimidin-4-one **(3)** (2 moles) condensed with cyanuric chloride to obtained **(7)**, which on condensation with different alkyl/aryl amines gave 2,4-bis (6'-p-anisyl-5'-cyano-3'-N-methyl-3',4'-dihydro-4'-oxopyrimidin-2'-ylhydrazino)-6-alkyl/aryl amino-s-triazine derivatives **(8a-i)**.While compound **(9)** (tris) obtained by condensation of **(7)** with compound **(3)** at 130^{0}C.

The constitution of all the products was established by elemental analyses, IR and NMR spectral study. All the compounds were screened *in vitro* for their antimicrobial activity against different strains of bacteria and fungi.

EXPERIMENTAL

All the melting points were taken in open capillaries and are uncorrected. Infrared spectra (KBr) were re-

corded on a Shimadzu-435-IR Spectrophotometer and ^{1}H PMR Spectra on Bruker Spectrometer (300 MHz) using TMS as an internal reference.

6-p-Anisyl-5-cyano-2-mercapto-3, 4-dihydropy rimidin-4-one (1)

A mixture of ethylcyano acetate (5.7g, 0.05M), thiourea (3.8, 0.05M), p-anisaldehyde (6.8g, 0.05M), potassium carbonate (6.9g, 0.05M) in absolute alcohol (50 ml) was refluxed for 12 hrs. and cooled. The precipitate was poured into cold water and neutralized with glacial acetic acid, the product obtained was filtered off and washed with water, crystallized from methanol: DMF mixture, yield 52%, M.P. 245^{0}C. Calcd. for $C_{12}H_9N_3O_2S$: C 55.59, H 3.47, N 16.21%. Found C 55.52 H 3.31, N 16.14 %. IR ν max (KBr) : 3092 (C-H str.), 2240(C=N str.), 1670 (C=O str.), 1545 (C=N str.), 1215 (C-O str.) cm^{-1}. ^{1}H PMR δppm ($CDCI_3$) : 3.88 (s, 3H, -OCH_3), 6.98-8.92 (m,6H, Ar-H, -NH and -SH).

6-p-Anisyl-5-cyano-2-methylthio-3-N-methyl-3, 4-dihyropyrimidine-4-one (2)

To a solution of 6-p-anisyl-5-cyano-2-mercapto-3, 4-dihydrophyrimidin-4-one **(1)** (2.59g, 0.01M) in DMF (20 ml), potassium carbonate (2.76g, 0.02 M) and methyl iodide (2.84g, 0.02M) were added and stirred for 3 hrs. The reaction mixture was diluted with cold water and neutralized by glacial acetic acid. The product was isolated and crystallized from dioxane, yield 68%. M.P. 197^{0}C. Calcd. for $C_{14}H_{13}N_3O_2S$; C 58.53, H 4.52, N 14.63 %. Found C 58.45, H 4.52, N 14.31 %. IR *ν* max (KBr) 3012 (C-H str.), 2216 (C=N str.), 1662 (C=0 str.), 1542 (C=N str.), 1267 (C-O str.), 572 (C-S str.)cm^{-1} ^{1}H PMR δ ppm ($CDCI_3$) : 2.71 (s 3H, -SCH_3), 3.57 (s, 3H, -NCH_3), 3.88 (s, 3H, -OCH_3), 6.96-7.01 (d, J=9 Hz, 2H, Ar-H), 8.11-8, 16 (d, J=9 Hz, 2H, Ar-H).

6-p-Anisyl-5-cyano-2-hydrazino-3-N-methyl-3, 4-dihyropyrimidin-4-one (3)

A mixture of compound **(2)** (2.87 g, 0.01M) and hydrazine (0.96g, 0.03M) in absolute alcohol was refluxed for 10 hrs. The reaction mixture was poured in to ice. The product was isolated and crystallized from DMF, yield 59%. M.P. 262^{0}C. Calcd. for $C_{13}H_{13}N_5O_2$ C 57.56, H 4.79, N 25.83 %. Found C 57.51 H 4.76, N 25.79 %. IR *ν* max (KBr) : 3301 (N-H str.), 2942 (C-H str.), 2222 (C≡N str.), 1683 (C=O str.) 1613 (N-H str.), 1550 (C=N str.), 1265 (C-O str.) cm^{-1} : ^{1}H PMR δ ppm ($CDCl_3$) : 3.38 (s, 3H, -NCH_3), 3.89 (s, 3H, -OCH3), 6.95-7.09 (m, 7H, Ar-H, -NH).

TABLE 1: Antimicrobial activity of some selected compound which exhibited highest activity (inhibition zone = 16-26mm)

B.megaterium	*B.subtilis*	*E.coli*	*P.fluorescens*	*A.awamori*
6a-c, 6e, 6j, 6s, 6t, 6y, 8b, 9	6b, 6j, 6s, 8b	6a-p, 6r-w, 6y, 6z, 8a-i, 9	6a, 6c, 6e, 6f, 6g, 6I-q, 6s, 6w, 6z, 8f-i, 9	6b, 6c, 6f, 6h-j, 6l, 6q, 6t, 6v, 6x, 8a, 8c, 8d, 8h, 8i, 9

6-p-Anisyl-5-cyano-3-N-methyl-2(2', 4'-dichloro-s-triazin-6'-yl hydrazine)-3, 4-dihydropyrimidin-4-one (4)

6-p-Anisyl-5-cyano-2-hydrazino-3-N-methyl-3, 4-dihydropyrimidin-4-one **(3)** (2.71g, 0.01M) was added occasionally to cyanuric chloride (1.8g, 0.01M) dissolved in acetone (15 ml) at 0-5^{0}C, the contents were stirred for 3 hrs. with gradual addition of sodium bicarbonate to neutralize the acid evolved during the reaction. The reaction mixture was poured in crushed ice and filtered off, yield 63 %.

6-p-Anisyl-5-cyano-3-N-methyl-2(2', 0-anisyl amino-4'-chloro-s-triazin-6'-yl hydrazino)-3, 4-dihydropyrimidin-4-one (5e)

A mixture of 0-anisidine (1.23g, 0.01M) and compound 4 (4.19g, 0.01M) in acetone (20 ml) was stirred at 30-35^{0}C for 3 hrs. with gradual addition of sodium bicarbonate to neutralize the acid evolved during reaction. The reaction mixture poured in ice and product was isolated, crystallized from dioxane, yield 58%. M.P. 265^{0}C.

6-p-Anisyl-5-cyano-3-N-methyl-2- (2'- o-anisyl amino-4'-m-anisyl amino-s-triazin-6'-yl hydrazino)-3, 4-digydropyrimidin-4-one (6z)

A mixture of m-anisidine (1.23g, 0.01M) and compound **(5)** (4.27g, 0.01M) in dioxane (25 ml) was refluxed for 6 hrs. at 110^{0}C. The contents were poured in to crushed ice. The product was isolated and crystallized from methanol : DMSO (2:1), yield 55%. M.P. 210^{0}C. Calcd. for $C_{30}H_{28}N_{10}O_4$:C 60.81, H 4.72, N 23.64%. Found C 60.79 H 4.71, N 23.61%. IR ν max (KBr) : 3330 (N-H str.), 2962 (C-H str.), 2196

TABLE 2: Physical data of compounds (6a-z)

Compd.	R	R^I	Molecular formula	M.P. (C°)	Yield (%)	% of N	
						Calcd.	Found
(6a)	$-C_2H_5$	$-C_6H_5$	$C_{24}H_{24}N_{10}O_2$	208	65	28.92	28.89
(6b)	$-C_2H_5$	2,3-$(CH_3)_2$-C_6H_3-	$C_{26}H_{28}N_{10}O_2$	255	59	27.34	27.31
(6c)	$-C_2H_5$	3-OCH_3-C_6H_4-	$C_{25}H_{26}N_{10}O_3$	208	49	27.23	27.18
(6d)	$-C_2H_5$	$-CH_2-C_6H_5$	$C_{25}H_{26}N_{10}O_2$	200	57	28.11	28.01
(6e)	$-C_2H_5$	3-CH_3-C_6H_4-	$C_{25}H_{26}N_{10}O_2$	190	41	28.11	28.07
(6f)	$-C_2H_4-N(C_2H_5)_2$	3, 5-$(CH_3)_2$-C_6H_3-	$C_{30}H_{37}N_{11}O_2$	240	63	26.41	26.39
(6g)	$-C_2H_4-N(C_2H_5)_2$	2-C_4H_3O-	$C_{26}H_{31}N_{11}O_3$	155	61	28.25	28.21
(6h)	$-C_2H_4-N(C_2H_5)_2$	2-OCH_3-C_6H_4-	$C_{29}H_{35}N_{11}O_3$	255	52	26.32	26.27
(6i)	$-C_2H_4-N(C_2H_5)_2$	3-OCH_3-C_6H_5-	$C_{29}H_{35}N_{11}O_3$	285	65	26.32	26.28
(6j)	$-C_2H_4-N(C_2H_5)_2$	$-CH_2-C_6H_4$-	$C_{29}H_{35}N_{11}O_2$	150	58	27.06	27.00
(6k)	3-Cl, 4-F-C_6H_3-	3-Cl-C_6H_4-	$C_{28}H_{21}N_{10}O_2FCl_2$	>300	56	22.69	22.67
(6l)	3-Cl, 4-F-C_6H_3-	2, 6-$(CH_3)_2$-C_6H_3-	$C_{30}H_{26}N_{10}O_2FCl$	>300	64	22.89	22.78
(6m)	3-Cl, 4-F-C_6H_3-	$-C_2H_5$	$C_{24}H_{22}N_{10}O_2FCl$	268	52	26.14	26.08
(6n)	3-Cl, 4-F-C_6H_3-	2-C_4H_3O-	$C_{26}H_{20}N_{10}O_3FCl$	255	53	24.41	24.32
(6o)	3-Cl, 4-F-C_6H_3-	2-OCH_3-C_6H_4-	$C_{29}H_{24}N_{10}O_3FCl$	295	62	22.81	22.71
(6p)	3-Cl, 4-F-C_6H_3-	3-OCH_3-C_6H_4-	$C_{29}H_{24}N_{10}O_3FCl$	290	57	22.81	22.72
(6q)	2, 4-$(CH_3)_2$-C_6H_3-	3-Cl-C_6H_4	$C_{30}H_{27}N_{10}O_2Cl$	120	59	23.54	23.49
(6r)	2, 4-$(CH_3)_2$-C_6H_3-	2, 6-$(CH_3)_2$-C_6H_3-	$C_{32}H_{32}N_{10}O_2$	195	63	23.80	23.76
(6s)	2, 4-$(CH_3)_2$-C_6H_3-	3, 5-$(CH_3)_2$-C_6H_3-	$C_{32}H_{32}N_{10}O_2$	195	57	23.80	23.79
(6t)	2, 4-$(CH_3)_2$-C_6H_3-	2-OCH_3-C_6H_4-	$C_{31}H_{30}N_{10}O_3$	172	61	23.72	23.68
(6u)	2, 4-$(CH_3)_2$-C_6H_3-	$-CH_2-C_6H_5$	$C_{31}H_{30}N_{10}O_2$	184	54	24.39	24.38
(6v)	2-OCH_3-C_6H_4 -	2, 6-$(CH_3)_2$-C_6H_3-	$C_{31}H_{30}N_{10}O_3$	242	59	23.72	23.66
(6w)	2-OCH_3-C_6H_4 -	$-C_2H_5$	$C_{25}H_{26}N_{10}O_3$	230	47	27.23	27.21
(6x)	2-OCH_3-C_6H_4 -	2-C_4H_3O-	$C_{27}H_{24}N_{10}O_4$	170	52	25.36	25.33
(6y)	2-OCH_3-C_6H_4 -	2-OCH_3-C_6H_4-	$C_{30}H_{28}N_{10}O_4$	220	67	23.64	23.58
(6z)	2-OCH_3-C_6H_4 -	3-OCH_3-C_6H_4-	$C_{30}H_{28}N_{10}O_4$	210	55	23.64	23.61

(C=N str.), 1674 (C-O str.) 771 (N-H str.).cm^{-1} ^1H PMR δ ppm ($CDCl_3$) : 3.56 (s, 3H, $-NCH_3$), 3.78 [s, 6H, 2X(-NH-Ar-OCH3)], 3.89 (s, 3H,Ar-OCH3), 6.84-7.59 [m, 16H, 12X(Ar-H) and 4X(-NH).

Similarly other compounds of type 6 were prepared. The physical data are recorded in TABLE 2.

2,4-Bis (6'-p-anisyl-5'-cyano-3'-N-methyl-3', 4'-dihydro-4'- oxopyrimidin-2'-yl hydrazino)-6-chloro-s-triazine (7)

Compound **(3)** (5.42g, 0.02M was added occasionally to cyanuric chloride (1.84g; 0.01M) dissolved in acetone (50 ml). The contents were stirred at 30-35^{0}C for 3 hrs. with gradual of sodiumbicarbonate to neutralize the acid evolved during the reaction. The reaction mixture then poured in to ice and filtered off, crystallized from dioxane, yield 57%, M.P. 286^{0}C.

2,4-Bis (6'-p-anisyl-5'-cyano-3'-N-methyl-3', 4'-dihydro-4'- oxopyrimidin-2'-yl hydrazino)- -6-ethylamino-s-triazine (8a)

A mixture of compound **(7)** (6.53g, 0.01M) and ethylamine (0.45g, 0.01M) in dioxane (50 ml) was refluxed for 6 hrs. at 110^{0}C. The contents were poured in to crushed ice. The product was isolated and crystallized from dioxane, yield 57%. M.P. 205^{0}C. Calcd. for $C_{31}H_{30}N_{14}O_4$:C 56.19, H 4.53, N 29.60%. Found C 56.12 H 4.49, N 29.55%. IR ν max (KBr) : 3380 (N-H str.), 2963 (C-H str.), 2224 (C=N str.), 1685, 1665 (C=O str.), 700 (C-N str.). cm^{-1}. ^1H PMR δ ppm ($CDCl_3$) : 1.22-1.25 (t, 3H, CH_2-CH_3), 3.36 [s, 6H, 2x($-NCH_3$)], 3.59-3.70 (q, 2H, - CH_2 - CH_3), 3.89 [s, 6H, 2X($-OCH_3$)], 6.96-7.37 (m, 8H, Ar-H), 7.60 – 7.84 [m, 5H, 5X(-NH)].

Similarly other compounds of type 8 were prepared. The physical constants are recorded in TABLE 3.

2,4,6-Tris (6'-p-anisyl-5'-cyano-3'-N-methyl-3', 4'-dihydro- 4' -oxopyrimidin-2'-yl hydrazino)-s-triazine (9)

A mixture of compound 7 (6.53g, 0.01M) and compound **(3)** (2.71g, 0.01M) in dioxane (75 ml) was refluxed for 8 hrs. at 130^{0}C. The reaction mixture was poured in ice. The obtained product was isolated and

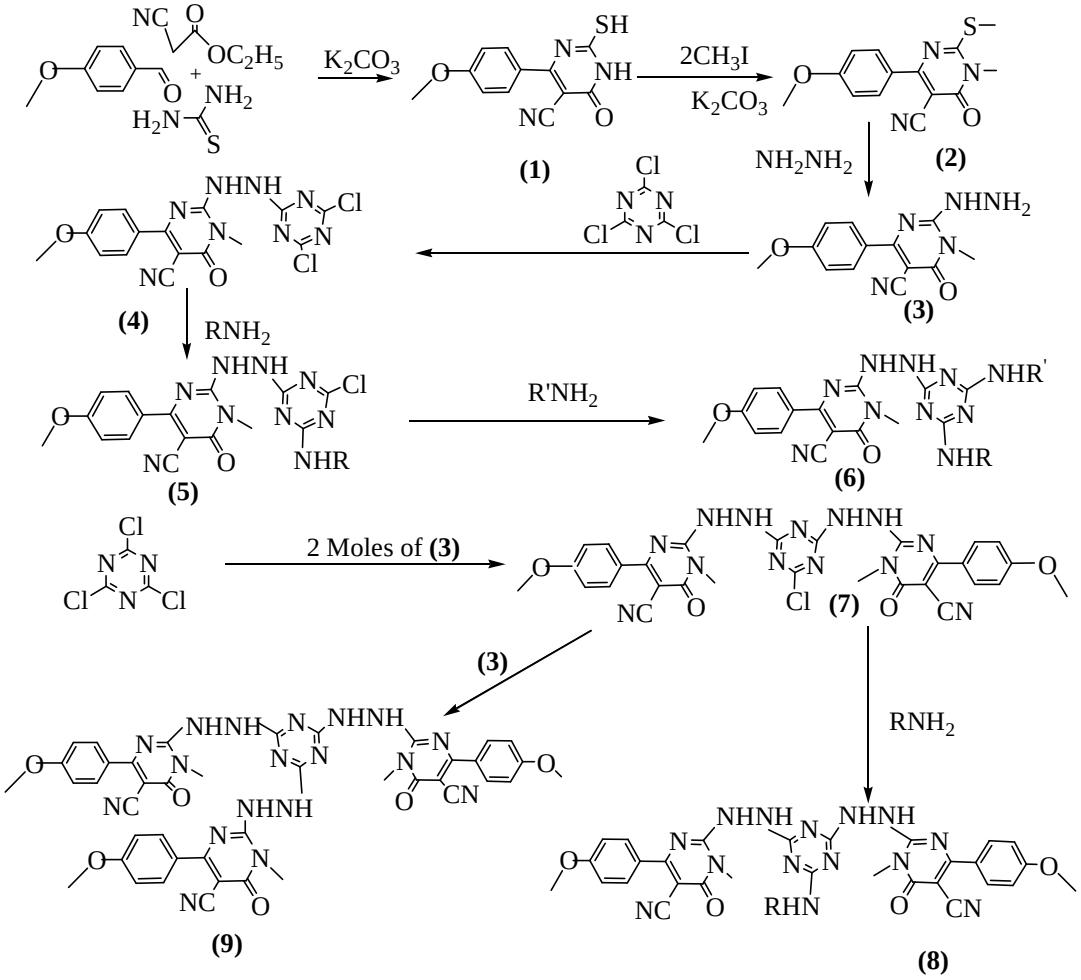
crystallized from dioxane : DMSO (2:1), yield 64%. M.P. 242^{0}C. Clacd for $C_{42}H_{36}N_{18}O_6$:C 56.75, H 4.05, N 28.37%. Found C 56.72 H 4.01, N 28.32%. IR ν max (KBr) : 3415 (N-H str.), 3020 (C-H str. Ar), 2960 (C-H str.), 2240 (C≡N str.), 1668 broad (C=O str.) 750 (C-N str.) ^{1}H PMR δ ppm ($CDCl_3$) : 3.27-3.59 [t, 9H, 3X(-NCH_3)], 3.82-3.89 [t, 9H, 3X(-OCH_3)], 6.90-7.89 (m, 18H, 12X(Ar-H) and 6X(-NH)]. The physical constants are recorded in TABLE 3.

TABLE 3 : Physical data of compounds (8a-i) and **(9)**

Compd.	R	Molecular formula	M.P. (C°)	Yield (%)	% of N Calcd.	% of N Found
(8a)	-C_2H_5	$C_{31}H_{30}N_{14}O_4$	205	57	29.60	29.55
(8b)	-CH_2-C_6H_5	$C_{36}H_{32}N_{14}O_4$	232	52	27.07	27.00
(8c)	-C_6H_5	$C_{35}H_{30}N_{14}O_4$	275	43	27.60	27.56
(8d)	3-Cl-C_6H_4 -	$C_{35}H_{29}N_{14}O_4Cl$	282	53	26.32	26.28
(8e)	2, 6-$(CH_3)_2$-C_6H_3-	$C_{37}H_{34}N_{14}O_4$	>300	44	26.55	26.49
(8f)	2-C_4H_3O	$C_{33}H_{28}N_{14}O_5$	205	61	28.00	27.98
(8g)	2-OCH_3-C_6H_4 -	$C_{36}H_{32}N_{14}O_5$	275	43	26.48	26.44
(8h)	3-OCH_3-C_6H_4 -	$C_{36}H_{32}N_{14}O_5$	>300	52	26.48	26.47
(8i)	2-$C_4H_3N_2$-	$C_{33}H_{28}N_{16}O_4$	269	55	31.46	31.41
(9)	-	$C_{42}H_{36}N_{18}O_6$	242	64	28.37	28.32

In vitro evaluation of biological studies

The antimicrobial activity assay was carried out using cup-plate agar diffusion method by measuring the zones of inhibition in mm. All the compounds were screened *in vitro* for their antimicrobial activity against variety of bacterial strains such as *Bacillus megaterium, Bacillus subtilis, Escherichia coli, Pseudomonas fluorescens* and fungi, *Aspergillus awamori* at a concentration of 50μg, known antibiotics were used for comparision, which displayed zone of inhibition like



SCHEME 1

Ampicillin (14-25 mm), Chloramphenicol (15-20 mm) and Norfloxacin (15-27 mm) against bacterial strains and griseofulvin showed zone of inhibition (13-23 mm) against fungi *A.awamori.*

From the screening result of the antibacterial activity, It can be concluded that compound **(6t)** and **(8b)** showed highest activity against *B.mega.* Compounds **(6b, 6e, 6f,6g, 6i, 6j, 6I-0**, **6r-t, 6v, 6w, 6y, 6z, 8a, 8c, 8e-i, 9)** and **(6f, 6n-p, 6q, 8g)** exhibited significant activity against *E.coli* and *P.fluorescens* respectively. In case of anti-fungal activity compounds **(6b, 6t)** and **(8a)** observed highly active against *A.awamori.*

The compounds (**6a, 6g, 6q, 8a)** and **(8c)** have been selected for their agricultural and pharmacological screening by Du Pont Agricultural products U.S.A. Ampicillin (14-25mm), Chloramphenicol (15-20mm), Norfloxacin (15-27 mm), Grisefulvin (13-23 mm).

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