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SYNTHESIS , CHARACTERISATION AND ANTIBACTERIAL ACTIVITY OF SOME NOVEL ISOXAZOLES, PYRIMIDINTHIONES AND PYRIMIDINONES

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ABSTRACT

The title compounds **(7a-e)**, **(8a-e)** and **(9a-e)** have been prepared from chalcones **(6a-e)** having *s*-triazine nucleus. These chalcones on cyclisation with hydroxyl amine hydrochloride in the presence of alkali give isoxazoles **(7a-e)**. Chalcones **(6a-e)** on condensation with thiourea and urea in the presence of alkali give pyrimidinthiones **(8a-e)** and pyrimidinones **(9a-e)** respectively. Structures of newly synthesised compounds were established on the basis of their elemental analysis, IR and ^{1}H NMR spectral data. All the synthesised compounds have been screened for their antibacterial activity.

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KEYWORDS

Isoxazoles, Pyrimidinthiones, Pyrimidinones, Spectral data, Antibacterial activity.

INTRODUCTION

Among a wide variety of heterocycle that have been explored for developing pharmaceutical important molecules such as isoxazoles, pyrimidinethiones and pyrimidinones have played an important role in medicinal chemistry. Various biological applications have been reported for isoxazoles such as antileukemia[1], neuroleptic[2], anticonvulsant[3] and antagonistic[4]. Pyrimidinethiones have been found to possess antitubercular[5], antitumor[6] and hypoglycamic[7] activities. During the past years, considerable evidences have been accumulated to demonstrate the potential of pyrimidinones incorporating variety of biological activities such as anticancer[8], antimicrobial[9] and analgesic[10]. In view of the above and in continuation of our work[11-13], we herein report a new series of isoxazoles **(7a-e)**, pyrimidinethiones **(8a-e)** and pyrimidinone **(9a-e)**. The synthesised compounds were screened for their *in vitro* antibacterial activity against four different bacterial strain viz *S. aureus* (MTCC 96), *B. Subtilis* (MTCC 441) [Gram-positive bacteria] and *E. coli* (MTCC 443), *S. Paratyphi-B* (MTCC 733) [Gram-negative bacteria] by agar diffusion method.

MATERIALS AND METHODS

All melting points were determined in an open capillary and are uncorrected. The IR spectra were recorded on a FTIR - 8400 spectrometer and ^{1}H NMR spectra on a Bruker Avance DPX 400 MHz spectrometer with $CDCl_3$ as a solvent and tetramethylsilane (TMS) as internal standard. The chemical shifts are expressed in parts per million (ppm) downfield from the internal standard and signals are quoted as *s* (singlet) and *m* (multiplate). Analytical separation was conducted with silica Gel 60 F-254 (Merck) plates of 0.25 mm thickness eluted with toluene : acetone (10 : 2 v/v) and were visualized with UV (254 nm) or iodine to check the purity of the synthesised compounds.

General procedure for the compounds (3), (4), (5) and (6). Compounds (3), (4), (5) and (6) were prepared by the reported method[14].

Preparation of 2-phenylamino-4-(4'-chlorophenylamino)-6-[4'-{5"-(4"'-methoxyphenyl) – isoxazole - 3"-yl} phenyl amino]-s-triazine (compound 7a) : *Compound* ***6a*** *(0.01 mole) was* dissolved in ethyl alcohol (25 ml) and hydroxylamine hydrochloride (0.01 mole) was added to it. Then solution of 40% KOH was added to the reaction mixture and refluxed for 10 hours. The progress of the reaction was monitored on TLC plate. After complition, the reaction mixture was cooled and poured into crushed ice and neutralized with dilute HCl. The product separated out was filtered, washed with water, dried and recrystallised from alcohol to give **7a**.

Similarly, the remaining compounds **7(b-g)** were prepared by this method. Their physical data are given in **Table-1**.

Compound (7a) Yield 65%, m.p.125ºC. Anal. Calcd. For $C_{31}H_{24}ClN_7O_2$: C, 66.25; H, 4.30; N, 17.45. Found: C: 66.20; H: 4.24; N: 17.41%; IR (KBr,cm^{-1}): 3368 (N-H str.), 3135 (=CH str.), 1585 (C=N str., isoxazole moiety), 1507 (C=C str.), 1033 (C-O-C str.), 808 (C-N str., *s*-triazine moiety), 771 cm^{-1} (C-Cl str.) ; ^{1}H NMR ($CDCl_3$, δ, ppm): 3.81 (3H, *s*, O-OCH_3), 4.0 (3H, *s*, NH), 6.79 (1H, *s*, -CH,

isoxazole moiety), 6.98 – 7.91 (17H, *m*, Ar-H).

Preparation of 2-phenylamino-4-(4'-chlorophenylamino)-6-[4'-{2"-mercapto-6"-(3"',4"'- dimethoxyphenyl)–pyrimidin - 4"-yl}phenylamino]-s-triazine (compounds 8a) : Compound **6a** (0.01 mole) was dissolved in ethyl alcohol (25 ml) and thiourea (0.01 mole) was added to it. Then solution KOH (5 ml of 40%) was added to the reaction mixture and refluxed for 8 hours. The progress of the reaction was monitored on TLC plate. After completion, the reaction mixture was cooled and poured into crushed ice and neutralized with dilute HCl. The product separated out was filtered, washed with water, dried and recrystallised from alcohol to give **8a**.

Similarly, the remaining compounds **8(b-g)** were prepared by this method. Their physical data are given in **Table-1**.

Compound (8a) Yield 72%, m.p.175ºC. Anal. Calcd. For $C_{32}H_{25}ClN_8OS$: C, 63.52; H, 4.16; N, 18.52. Found: C: 63.48; H: 4.12; N: 18.50%; IR (KBr, cm^{-1}): 3398 (N-H str.), 3311 (=CH str.), 1572 (-SH str., pyrimidine moiety), 807 (C-N str., *s*-triazine moiety), 753 cm^{-1} (C-Cl str.) ; ^1H NMR ($CDCl_3$, δ, ppm): 3.4 (1H, *s*, -SH), 3.7 (3H, *s*, 2-OCH_3), 4.3 (3H, s, Ar-NH), 7.1 – 8.2 (18H, *m*, Ar-H + NH).

Preparation of 2-phenylamino-4-(4'-chlorophenylamino)-6-[4'-{2"-hydroxy-6"-(3"',4"'-methoxyphenyl)–pyrimidin - 4"-yl}phenylamino]-s-triazine (compound 9a) : *Compound* ***6a*** (0.01 mole) was dissolved in ethyl alcohol (25 ml) and urea (0.01 mole) was added to it. Then solution KOH (5 ml of 40%) was added to the reaction mixture and refluxed for 8 hours. The progress of the reaction was monitored on TLC plate. After completion, the reaction mixture was cooled and poured into crushed ice and neutralized with dilute HCl.The product separated out was filtered, washed with water, dried and recrystallised from alcohol to give **9a**.

Similarly, the remaining compounds **9(b-g)** were prepared by this method. Their physical data are given in **Table-1**.

Compound (9a) Yield 70%, m.p.118ºC. Anal. Calcd. For $C_{32}H_{25}ClN_8O_2$: C, 65.25; H, 4.27; N, 19.02. Found: C: 65.20; H: 4.22; N: 19.00%; IR (KBr,cm^{-1}): 3415 (N-H str.), 3340 (=CH str.), 3108 (-OH str., pyrimidine moiety), 819 (C-N str., *s*-triazine moiety), 750 cm^{-1} (C-Cl str.) ; ^1H NMR ($CDCl_3$, δ, ppm): 3.81 (3H, *s*, p-OCH_3), 4.0 (3H, *s*, NH), 7.0 – 8.0 (17H, *m*, Ar-H), 10.2 (1H, *s*, -OH).

Table-1

Characterization data of compounds 7(a-g), 8(a-g) and 9(a-g)

Compd	R	Molecular formula	m.p °C	Elemental Analysis		
				% C Found (Calcd.)	% N Found (Calcd.)	% H Found (Calcd.)
7a	2 - Methoxyphenyl	$C_{31}H_{24}ClN_7O_2$	125	66.22 (66.25)	17.30 (17.31)	4.28 (4.30)
7b	3 - Chlorophenyl	$C_{30}H_{21}Cl_2N_7O$	146	63.58 (63.61)	17.30 (17.31)	3.71 (3.73)
7c	4 - Chlorophenyl	$C_{30}H_{21}Cl_2N_7O$	152	63.60 (63.61)	17.30 (17.31)	3.69 (3.73)
7d	4 - Fluorophenyl	$C_{30}H_{21}ClFN_7O$	129	65.60 (65.62)	17.82 (17.83)	3.83 (3.85)
7e	4 - Methylphenyl	$C_{31}H_{24}ClN_7O$	137	68.17 (68.19)	17.95 (17.96)	4.41 (4.43)
7f	3 - Phenoxyphenyl	$C_{36}H_{26}ClN_7O_2$	125	69.25 (69.29)	15.70 (15.71)	4.17 (4.20)
7g	3,4 - Dimethoxyphenyl	$C_{32}H_{26}ClN_7O_3$	143	64.90 (64.92)	16.50 (16.56)	4.40 (4.42)
8a	2 - Methoxyphenyl	$C_{32}H_{25}ClN_8OS$	181	63.51 (63.52)	18.50 (18.52)	4.12 (4.16)
8b	3 - Chlorophenyl	$C_{31}H_{22}Cl_2N_8S$	165	61.04 (61.09)	18.34 (18.38)	3.62 (3.64)
8c	4 - Chlorophenyl	$C_{31}H_{22}Cl_2N_8S$	160	61.07 (61.09)	18.35 (18.38)	3.60 (3.64)
8d	4 - Fluorophenyl	$C_{31}H_{22}ClFN_8S$	95	62.77 (62.78)	18.84 (18.89)	3.71 (3.74)
8e	4 - Methylphenyl	$C_{32}H_{25}ClN_8S$	138	65.21 (65.24)	19.01 (19.02)	4.23 (4.28)
8f	3 - Phenoxyphenyl	$C_{37}H_{27}ClN_8OS$	142	66.58 (66.61)	16.76 (16.79)	4.05 (4.08)
8g	3,4 - Dimethoxyphenyl	$C_{33}H_{27}ClN_8O_2S$	178	62.40 (62.41)	17.62 (17.64)	4.25 (4.28)
9a	2 - Methoxyphenyl	$C_{32}H_{25}ClN_8O_2$	118	65.22 (65.25)	19.00 (19.02)	4.22 (4.27)
9b	3 - Chlorophenyl	$C_{31}H_{22}Cl_2N_8O$	165	62.70 (62.74)	18.85 (18.88)	3.71 (3.73)
9c	4 - Chlorophenyl	$C_{31}H_{22}Cl_2N_8O$	145	62.72 (62.74)	18.86 (18.88)	3.69 (3.73)
9d	4 - Fluorophenyl	$C_{31}H_{22}ClFN_8O$	180	64.52 (64.53)	19.40 (19.42)	3.80 (3.84)
9e	4 - Methylphenyl	$C_{32}H_{25}ClN_8O$	90	67.05 (67.07)	19.52 (19.55)	4.36 (4.39)
9f	3 - Phenoxyphenyl	$C_{37}H_{27}ClN_8O_2$	115	68.23 (68.25)	17.20 (17.21)	4.15 (4.18)
9g	*3,4 - Dimethoxyphenyl*	$C_{33}H_{27}ClN_8O_3$	*110*	*64.00 (64.03)*	*18.06 (18.10)*	*4.35 (4.39)*

Table 2
Antibacterial activity data of compounds 7(a-g), 8(a-g) and 9(a-g).

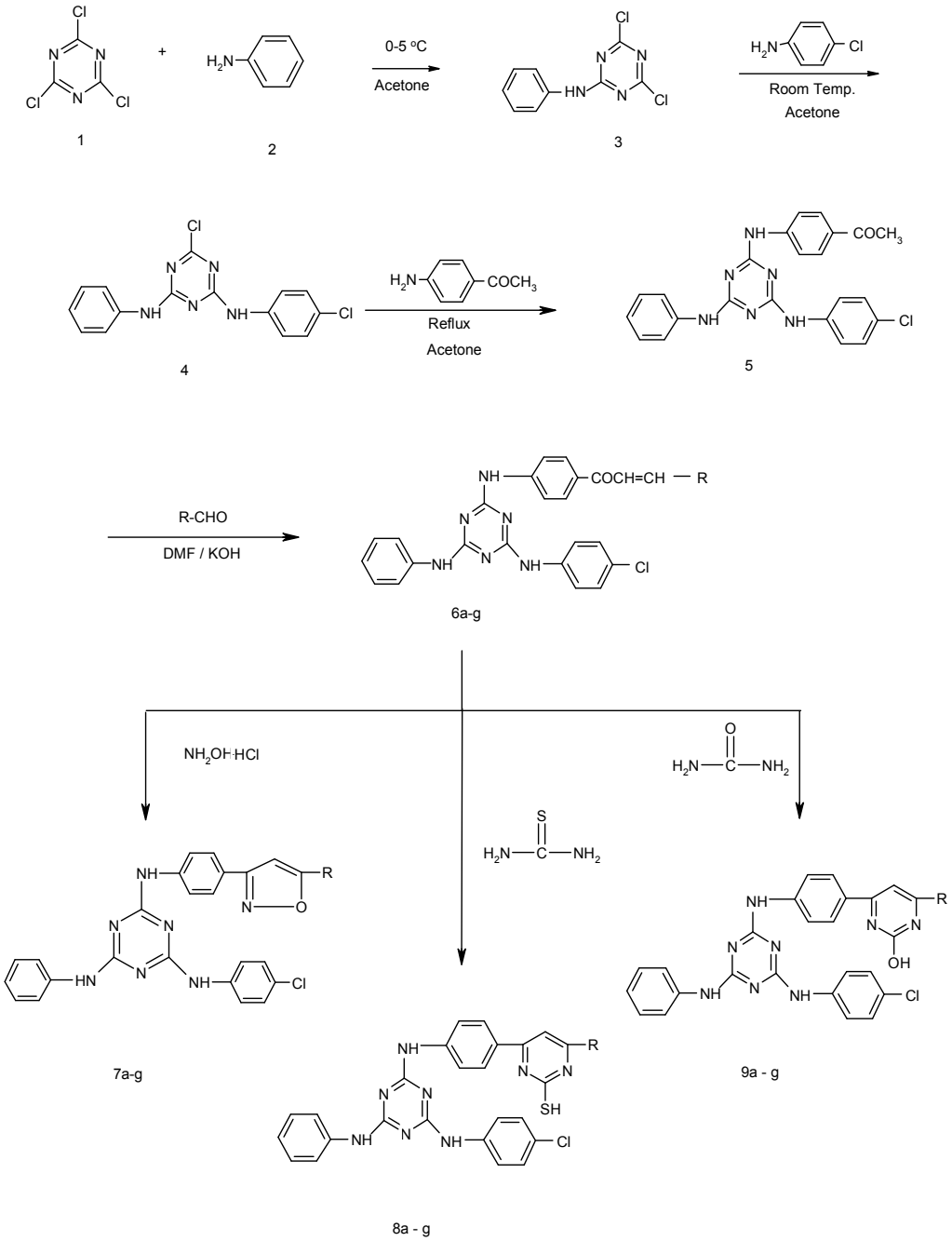
Compd .No.	R	Antibacterial Activity Diameter of zone of inhibition (in mm)			
		S.aureus MTCC-96	*B.subtilis* MTCC-441	*E.coli* MTCC-443	*S.paratyphi-B* MTCC-733
7a	2 - Methoxyphenyl	14	17	10	18
7b	3 - Chlorophenyl	-	19	21	20
7c	4 - Chlorophenyl	12	18	19	15
7d	4 - Florophenyl	14	15	19	13
7e	4 - Methylphenyl	15	14	18	17
7f	3 - Phenoxyphenyl	13	14	17	16
7g	3,4 - Dimethoxyphenyl	16	15	13	16
8a	2 - Methoxyphenyl	17	18	19	17
8b	3 - Chlorophenyl	18	16	18	-
8c	4 - Chlorophenyl	17	15	17	16
8d	4 - Florophenyl	15	18	14	16
8e	4 - Methylphenyl	18	15	14	18
8f	3 - Phenoxyphenyl	15	20	18	17
8g	3,4 - Dimethoxyphenyl	17	11	19	-
9a	2 - Methoxyphenyl	13	16	18	17
9b	3 - Chlorophenyl	16	19	19	18
9c	4 - Chlorophenyl	17	20	20	19
9d	4 - Florophenyl	17	17	21	19
9e	4 - Methylphenyl	15	16	20	16
9f	3 - Phenoxyphenyl	18	19	15	15
9g	3,4 - Dimethoxyphenyl	16	18	17	17
	Standard Drug Ciprofloxacin	22	24	25	26

RESULTS AND DISCUSSION

All the synthesized compounds were screened for their antibacterial activity by using agar diffusion method[15] against *S.aureus* (MTCC 96) and *B. subtilis* (MTCC 441) Gram positive bacteria and *E-coli* (MTCC 443), *S. paratyphi-B* (MTCC 733) Gram negative bacteria in nutrient agar medium. Ciprofloxacin was used as standard drug for the comparison of antibacterial activity.

The screening results indicate that the compounds **8b, 8e,** and **9f** were found to be active against *S. aureus* (MTCC-96). The compounds **7a, 7d, 7e, 7g, 8a, 8c, 8d, 8f, 8g, 9b, 9c, 9d, 9e** and **9g** were found to be moderately active against *S. aureus* (MTCC-96), whereas remaining compounds were found to be less active against same bacteria. The compounds **7b, 7c, 8a, 8d, 8f, 9b, 9c, 9f** and **9g** were found to be active against *B. subtilis* (MTCC-441). The compounds **7a, 7d, 7e, 7f, 7g, 8b, 8c, 8e, 9a, 9d** and **9e** were found to be moderately active against *B.*

subtilis (MTCC-441), whereas remaining compounds were found to be less active against same bacteria. The compound **7b** and **9d** was found to be active against *E. coli* (MTCC-443). The compounds **7c, 7d, 7e, 7f, 8a, 8b, 8c, 8e, 8f, 8g 9a, 9b, 9c, 9e** and **9g** were found to be moderately active against *E. coli* (MTCC-443). The compounds **7a, 7b, 7e,7f, 7g, 8a, 8c, 8d, 8e, 8f, 9a, 9b, 9c, 9d, 9e** and **9g** were found to be moderately active against *S. paratyphi-B* (MTCC-733) , whereas the remaining compounds were found to be less active against *S. paratyphi-B* (MTCC-733)



1 2 3 4 5 6a-g 7a-g 8a - g 9a - g

SCHEME -1

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