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An Efficient Synthesis 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 pyrimidin-2-ones **(9a-e)** respectively. Structures of newly synthesised compounds were established on the basis of their elemental analysis, IR and ^1H NMR spectral data. All the synthesised compounds have been screened for their antibacterial activity.*

Keywords: Isoxazoles, pyrimidinethiones, pyrimidinones, spectral data, antibacterial activity.

INTRODUCTION

Five membered heterocycles like isoxazoles have found wide application as pharmaceutical and agrochemical agents. The synthesis of isoxazole derivatives has attracted considerable attention from organic and medicinal chemists due to their considerable bioactivity. Various biological applications have been reported for isoxazoles such as antitumor [1], analgesic [2], antimicrobial [3] and chemotherapy [4]. Pyrimtdinethiones have been found to possess antiparasitic [5], antitumor [6] and hypoglycaemic [7] activities. During the past years, considerable evidence have been accumulated to demonstrate the potential of pyrimidinones incorporating variety of biological activities such as anticancer [8], anticonvulsant [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)**, pyrimidinthiones **(8a-e)** and pyrimidin-2-ones **(9a-e)**. The structure of all the synthesised compounds has been established on the basis of physical data, elemental analysis and spectral data. The synthesised compounds were screened for their *in vitro* antibacterial activity against four different 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 open capillary and are uncorrected. The IR spectra were recorded on a FTIR - 8400 spectrometer. ^{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 synthesized 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 (7g) : Compound **6g** (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 hrs. The progress of the reaction was monitored on TLC plate. After complition the reaction mixture was then cooled and poured into crushed ice and neutralized with dilute HCl. The product separated out was filtered, washed with water, dried and recrystallized from alcohol to give **7g**.

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

Compounds (7g) Yield 68%, m.p.196ºC: IR (KBr,cm^{-1}): 3360 (N-H str.), 3130 (=CH str.), 1580 (C=N str., isoxazole moiety), 1509 (C=C str.), 1036 (C-O-C str.), 809 (C-N str., *s*-triazine moiety), 781 cm^{-1} (C-Cl str.) ; ^{1}H NMR ($CDCl_3$, δ, ppm): 3.97 (3H, *s*, p-OCH_3), 6.70 (1H, *s*, -CH, isoxazole moiety), 6.90 – 7.80 (20H, *m*, Ar-H + NH). Anal. Calcd. For $C_{31}H_{24}ClN_7O_2$: C, 66.25; H, 4.30; N, 17.45. Found: C: 66.30; H: 4.24; N: 17.50%.

Preparation of 2-phenylamino-4-(4′-chlorophenylamino)-6-[4′-{2″-mercapto-6″-(3‴,4‴-dimethoxyphenyl)–pyrimidin - 4″-yl}phenylamino]-*s*-triazine (8g) : Compound **6g** (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 hrs. The progress of the reaction was monitored on TLC plate. After complition the reaction mixture was then 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 **8g**.

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

Compounds (8g) Yield 72%, m.p.178ºC: IR (KBr,cm^{-1}): 3390 (N-H str.), 3310 (=CH str.), 1578 (-SH str., pyrimidine moiety), 803 (C-N str., *s*-triazine moiety), 756 cm^{-1} (C-Cl str.) ; ^{1}H NMR ($CDCl_3$, δ, ppm): 3.4 (1H, *s*, -SH), 3.8 (3H, *s*, p-OCH_3), 7.0 – 8.0 (20H, *m*, Ar-H + NH). Anal. Calcd. For $C_{33}H_{27}ClN_8O_2S$: C, 62.41; H, 4.28; N, 17.64. Found: C: 62.48; H: 4.22; N: 17.60%.

Preparation of 2-phenylamino-4-(4′-chlorophenylamino)-6-[4′-{2″-hydroxy-6″-(3‴,4‴-methoxyphenyl)–pyrimidin - 4″-yl}phenylamino]-*s*-triazine (9g) : Compound **6g** (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 hrs. The progress of the reaction was monitored on TLC plate. After complition the reaction mixture was then 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 **9g**.

Table-1 Characterization data of compounds (7a-g), (8a-g) and (9a-g)

Compd	R	m.p °C	*Elemental Analysis*		
			% C Found (Calcd.)	% N Found (Calcd.)	*% H Found (Calcd.)*
7a	Phenyl	140	67.77 (67.73)	18.48 (18.43)	*4.10 (4.16)*
7b	2 - Chlorophenyl	116	63.64 (63.61)	17.38 (17.31)	*3.78 (3.73)*
7c	2 - Nitrophenyl	152	62.40 (62.45)	19.38 (19.42)	*3.62 (3.67)*
7d	3 - Nitrophenyl	157	62.49 (62.45)	19.37 (19.42)	*3.61 (3.67)*
7e	4 - Nitrophenyl	148	62.51 (62.45)	19.45 (19.42)	*3.71 (3.67)*
7f	3 – Bromophenyl	121	58.90 (58.98)	16.10 (16.05)	*3.40 (3.46)*
7g	4 – Methoxyphenyl	196	66.30 (66.25)	17.50 (17.45)	*4.24 (4.30)*
8a	Phenyl	181	64.80 (64.74)	19.52 (19.48)	*4.08 (4.03)*
8b	2 - Chlorophenyl	132	61.14 (61.09)	18.42 (18.38)	*3.70 (3.64)*
8c	2 - Nitrophenyl	146	60.10 (60.05)	20.38 (20.33)	*3.51 (3.58)*
8d	3 - Nitrophenyl	163	60.11 (60.05)	20.36 (20.33)	*3.52 (3.58)*
8e	4 - Nitrophenyl	135	60.09 (60.05)	20.37 (20.33)	*3.50 (3.58)*
8f	3 – Bromophenyl	125	56.88 (56.93)	17.20 (17.13)	*3.43 (3.39)*
8g	4 – Methoxyphenyl	172	63.48 (63.52)	18.57 (18.52)	*4.21 (4.16)*
9a	Phenyl	128	66.57 (66.61)	20.10 (20.05)	*4.10 (4.14)*
9b	2 - Chlorophenyl	135	62.70 (62.74)	18.91 (18.88)	*3.69 (3.73)*
9c	2 - Nitrophenyl	143	61.69 (61.64)	20.91 (20.87)	*3.71 (3.67)*
9d	3 - Nitrophenyl	138	61.68 (61.64)	20.93 (20.87)	*3.64 (3.67)*
9e	4 - Nitrophenyl	185	61.70 (61.64)	20.90 (20.87)	*3.72 (3.67)*
9f	3 – Bromophenyl	148	58.31 (58.37)	17.50 (17.57)	*3.40 (3.47)*

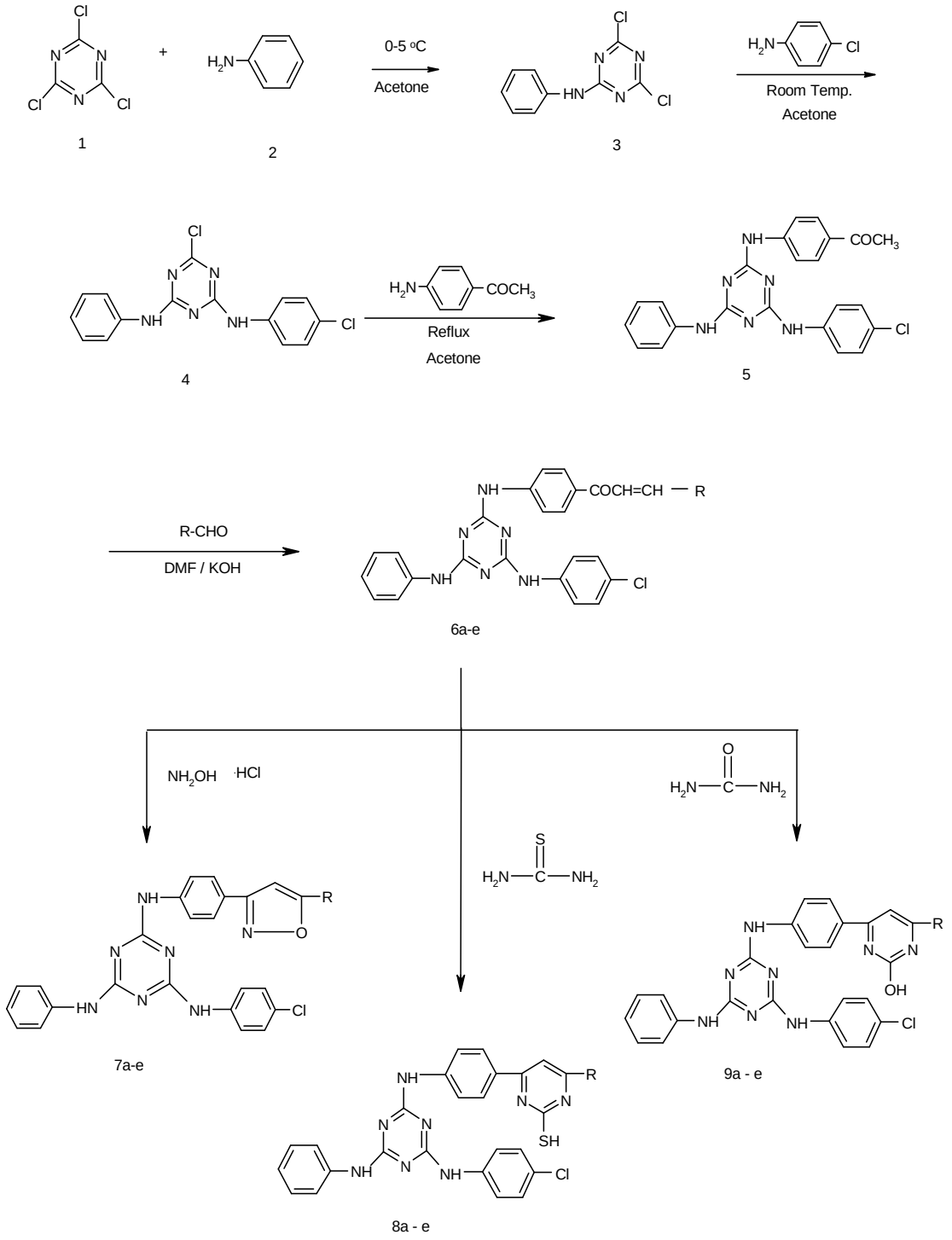
9g	*4 – Methoxyphenyl*	*168*	*65.21 (65.25)*	*19.06 (19.02)*	*4.23 (4.27)*

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

Compounds (9g) Yield 70%, m.p.110ºC: IR (KBr,cm^{-1}): 3410 (N-H str.), 3330 (=CH str.), 3100 (-OH str., pyrimidine moiety), 810 (C-N str., *s*-triazine moiety), 754 cm^{-1} (C-Cl str.) ; ^{1}H NMR ($CDCl_3$, δ, ppm): 3.85 (3H, *s*, p-OCH_3), 7.0 – 7.9 (20H, *m*, Ar-H + NH), 10.0 (1H, *s*, -OH). Anal. Calcd. For $C_{33}H_{27}ClN_8O_3$: C, 64.03; H, 4.39; N, 18.10. Found: C: 64.09; H: 4.32; N: 18.16%.

Table 2 – Antibacterial activity data of compounds (7a-g), (8a-g) and (9a-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	Phenyl	15	14	16	17
7b	2 - Chlorophenyl	11	13	21	15
7c	2 - Nitrophenyl	16	16	16	18
7d	3 - Nitrophenyl	14	18	17	16
7e	4 - Nitrophenyl	14	15	21	17
7f	3 – Bromophenyl	12	13	19	19
7g	4 – Methoxyphenyl	11	19	20	19
8a	Phenyl	15	17	17	15
8b	2 - Chlorophenyl	18	17	18	17
8c	2 - Nitrophenyl	18	15	17	17
8d	3 - Nitrophenyl	16	15	19	14
8e	4 - Nitrophenyl	17	17	17	15
8f	3 – Bromophenyl	15	18	17	14
8g	4 – Methoxyphenyl	17	17	19	16
9a	Phenyl	14	17	16	15
9b	2 - Chlorophenyl	14	12	20	17
9c	2 - Nitrophenyl	18	17	20	18
9d	3 - Nitrophenyl	17	18	20	16
9e	4 - Nitrophenyl	18	17	21	18
9f	3 – Bromophenyl	19	18	20	14
9g	4 – Methoxyphenyl	15	17	17	20
	Std. Drug Ciprofloxacin	22	24	25	26



SCHEME -1

RESULTS AND DISCUSSION

Antibacterial activity

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, 8c, 9c** and **9d** were found to be active against *S. aureus* (MTCC-96). The compounds **7a, 7c, 8a, 8d, 8e, 9a, 9b** and **9e** 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 **7e, 8d** and **9d** were found to be active against *B. subtilis* (MTCC-441). The compounds **7a, 7c, 8a, 8b, 8c, 8e, 9a, 9c** 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** was found to be active against *E. coli* (MTCC-443) whereas remaining compounds were found to be moderately active against *E. coli* (MTCC-443). The compounds **7a, 7c, 7e, 8b, 8c, 8e, 9b, 9c** and **9e** 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)

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