Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2012, 4(8):3778-3782

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis of some novel Isoxazole, Cyanopyridine and Pyrimidinthione derivatives

N. Solankee*, K. P. Patel and R. B. Patel

Department of Chemistry, B. K. M. Science College, Valsad-396001
(Affilated to TheVeer Narmad South Gujarat University, Surat). India

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ABSTRACT

*A new series of isoxazoles **(7a-d)**, cyanopyridines **(8a-d)** and pyrimidinthiones **(9a-d)** have been prepared from chalcones **(6a-d)** having s-triazine nucleus. These chalcones on cyclisation with hydroxyl amine hydrochloride in the presence of alkali and malononitrile in the presence of ammonium acetate give isoxazoles **(7a-d)** and cyanopyridines **(8a-d)** respectively. Chalcones **(6a-d)** on condensation with thiourea in the presence of alkali give pyrimidinthiones **(9a-d)**. Structures of newly synthesised compounds were established on the basis of their elemental analysis, IR and ^{1}H NMR spectral data.*

Keywords: Isoxazole, cyanopyridines, pyrimidinethiones, spectral data.

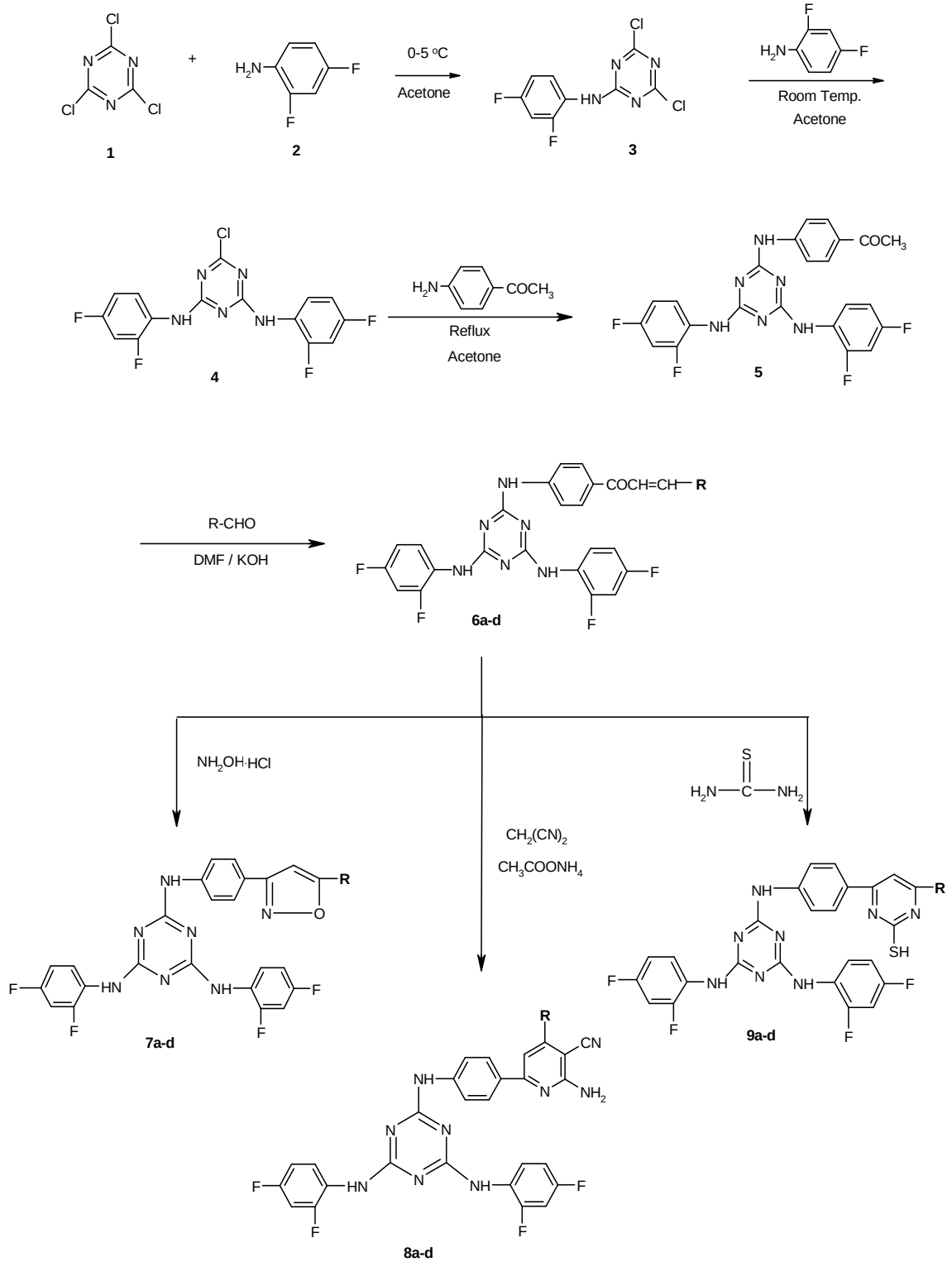
INTRODUCTION

Among a wide variety of heterocyclic that have been explored for developing pharmaceutical important molecules such as isoxazoles, cyanopyridines and pyrimidinethiones have played an important role in medicinal chemistry. Various biological applications have been reported for isoxazoles such as antitubercular [1], neuroleptic [2], anthelmintic [3], antibacterial [4] and antagonistic [5] etc… . Cyanopyridine derivatives have attracted considerable attention as they appeared of interest to possess anticonvulsant [6], antibacterial [7,8], antitumor [9], antihypertensive [10], cardiovascular [11] and antisoriasis [12] etc… activities. Pyrimidinethiones have been found to possess antitubercular [13], antitumor [14] and hypoglycemic [15] etc… activities. In view of the above and in continuation of our work [16-19], we herein report a new series of isoxazoles **(7a-d)**, cyanopyridines **(8a-d)** and pyrimidinethiones **(9a-d)**. The synthesised compounds were screened for their antimicrobial activity. The synthesised compounds were ascertained from spectral and physiochemical analysis. Results of IR and ^{1}H NMR analysis confirmed formation of the desired products.

EXPERIMENTAL SECTION

All melting points were determined in an open capillary and are uncorrected. The IR spectra were recorded on a FTIR - 8400 spectrophotometer. ^{1}H NMR spectra on a Bruker Avance DPX 400 MHz spectrometer with DMSO 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), *d* (doublet) and *m* (multiplate). Thin Layer Chromatography (TLC) analytical separation was conducted with Silica Gel 60 F-254 (Merck) plates of 0.25mm thickness eluted with toluene : acetone (10 : 4 v/v) and 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 [20].



SCHEME -1

Preparation of 2,4-bis-(2',4'-difluorophenylamino)-6-[4′-{5″-(2‴-chlorophenyl) – 2''- isoxazol-3''-yl} phenyl amino]-*s*-triazine (7a)

Compound **6a** (0.01 mol) was dissolved in alcohol (25 ml) and hydroxylamine hydrochloride (0.01 mol) was added to it. Then solution of 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 neutralised with dilute HCl. The product separated out was filtered, washed with water, dried and recrystallised from alcohol to give **7a**.

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

Compound (7a) IR (KBr,cm^{-1}) : 3410 (N-H str.), 3070 (=CH str.), 803 (C-N str., *s*-triazine moiety), 827 (C-H bending), 1624 (C=N str, isoxazole moiety), 1095 (C-F str.), 795 (C-Cl str.) ; ^{1}H NMR ($CDCl_3$, δ, ppm): 6.81 (1H, *s*, -CH=), 7.0 – 8.0 (17H, *m*, Ar-H and -NH).

Preparation of 2,4-bis-(2',4'-difluorophenylamino)-6-[4′-{2″-amino-3″-cyano-4″- (2‴-chlorophenyl) – pyridin-6''-yl} phenyl amino]-*s*-triazine (8a)

Compound **6a** (0.01 mol) was dissolved in alcohol (25 ml) and malononitrile (0.01 mol) was added to it. The reaction mixture was refluxed for 8 hours in presence of ammonium acetate. The progress of the reaction was monitored on TLC plate. After completion, the reaction mixture was cooled and poured into crushed ice and neutralised with dilute HCl. The product separated out was filtered, washed with water, dried and recrystallised from alcohol to give **8a**.

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

Compound (8a) IR (KBr,cm^{-1}) : 3415 (N-H str.), 3068 (=CH str.), 811 (C-N str, *s*-triazine moiety), 2050 (C=N str, cyanopyridine moiety), 1090 (C-F str.), 775 (C-Cl str.) ; ^{1}H NMR ($CDCl_3$, δ, ppm) : 6.8 (2H, *s*, -NH_2), 7.0 – 8.0 (18H, *m*, Ar-H and -NH).

Preparation of 2,4-bis-(2',4'-difluorophenylamino)-6-[4′-{2″- mercapto -6″-(2‴- chlorophenyl) – pyrimidin -4″-yl}phenylamino]-*s*-triazine (9a)

Compound **6a** (0.01 mol) was dissolved in alcohol (25 ml) and thiourea (0.01 mol) was added to it. Then solution of 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 neutralised with dilute HCl. The product separated out was filtered, washed with water, dried and recrystallised from alcohol to give **9a**.

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

Compound (9a) IR (KBr,cm^{-1}) : 3403 (N-H str.), 3075 (=CH str.), 805 (C-N str., *s*-triazine moiety), 825 (C-H bending), 1645 (C=N str, pyrimidine moiety), 1095 (C-F str.), 790 (C-Cl str.) ; ^{1}H NMR ($CDCl_3$, δ, ppm) : 11.1 (1H, *s*, -SH), 6.85 (1H, *s*, -CH=), 7.0 – 8.0 (17H, *m*, Ar-H and -NH).

RESULTS AND DISCUSSION

The IR spectrum of compound **7a** in KBr shows the characteristic band in the region of 1650-1580 cm^{-1} which indicate the presence of **-C=N** group. The IR spectrum of compound 8**a** shows characteristic band in region the of 2200-2000 cm^{-1} due to **–C=N** group. It also shows band in region the of 3500-3300 cm^{-1} due to **–NH_2** group. The IR spectrum of compound **9a** shows the characteristic band in the region of 1650-1570 cm^{-1} due to **(-C=N)**. ^{1}H NMR spectrum of compound **7a** shows singlet of **-CH=** at δ 6.81 confirmed the cyclisation in isoxazole moiety. The ^{1}H NMR spectrum of compound **8a** shows sharp singlet of **–NH_2** at δ 6.8 confirmed the present of amino group in cyanopyrimidine derivatives. The ^{1}H NMR spectrum of compound **9a** shows singlet of –SH group at δ 11.1 confirmed the pyrimidinethione moiety. Result of IR and ^{1}H NMR analysis confirmed formation of desired products.

Antibacterial activity

From the screening results **(Table – 2)**, The result shows that compounds **7a**, **7b**, **7c**, **7d** and **8a** exhibited good activity (25 – 125 µg/ml) against *E. coli* ; compounds **8a** and **9a** exhibited good activity (50 – 100 µg/ml) against *P. aeruginosa* . In Gram positive bacterial strains compounds **7c**, **8b** , **8c**, **9a**, **9b** and **9c** showed good to very good activity (25 – 150 µg/ml) against *S. aureus* ; where as compounds **8a** and **8c** showed good activity (62.5 – 100 µg/ml) against *S. pyogenes* compared with Ampicillin. All others compounds show moderately active or less active against all bacterial strains.

Antifungal activity

From the screening results **(Table – 2)**, Compounds **7b , 8a, 9a** and **9b** showed good activity against *C. albicans* compared with Griseofulvin, while compounds **8c** and **8d** showed very good activity against *C. albicans*.

Table -1 Characterisation data of compounds (7a-d), (8a-d) and (9a-d)

Comps	R	M. F	M.P °C	Elemental Analysis		
				% C Found (Calcd)	% N Found (Calcd)	% H Found (Calcd)
7a	2-Chlorophenyl	$C_{30}H_{18}ClF_4N_7O$	155	59.65 (59.66)	16.20 (16.23)	2.97 (3.00)
7b	3-Chlorophenyl	$C_{30}H_{18}ClF_4N_7O$	144	59.60 (59.66)	16.21 (16.23)	2.96 (3.00)
7c	4-Chlorophenyl	$C_{30}H_{18}ClF_4N_7O$	160	59.61 (59.66)	16.19 (16.23)	2.94 (3.00)
7d	2-Thienyl	$C_{28}H_{17}F_4N_7OS$	149	58.40 (58.43)	17.02 (17.04)	2.95 (2.98)
8a	2-Chlorophenyl	$C_{33}H_{20}ClF_4N_9$	118	60.55 (60.60)	19.22 (19.27)	3.02 (3.08)
8b	3-Chlorophenyl	$C_{33}H_{20}ClF_4N_9$	126	60.57 (60.60)	19.25 (19.27)	3.05 (3.08)
8c	4-Chlorophenyl	$C_{33}H_{20}ClF_4N_9$	135	60.53 (60.60)	19.21 (19.27)	3.04 (3.08)
8d	2-Thienyl	$C_{31}H_{19}F_4N_9S$	108	59.50 (59.52)	20.11 (20.15)	3.01 (3.03)
9a	2-Chlorophenyl	$C_{31}H_{19}ClF_4N_8S$	132	57.50 (57.54)	17.29 (17.32)	2.93 (2.96)
9b	3-Chlorophenyl	$C_{31}H_{19}ClF_4N_8S$	151	57.49 (57.54)	17.30 (17.32)	2.95 (2.96)
9c	4-Chlorophenyl	$C_{31}H_{19}ClF_4N_8S$	154	57.52 (57.54)	17.28 (17.32)	2.94 (2.96)
9d	2-Thienyl	$C_{29}H_{18}F_4N_8S_2$	140	62.54 (62.57)	17.14 (17.17)	3.68 (3.71)

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

Compounds	Minimal bactericidal concentration µg/ml				Minimal fungicidal concentration µg/ml		
	Gram negative		Gram positive				
	E. coli MTCC-443	*P. aerug* MTCC-1688	*S. aureus* MTCC-96	*S. pyogenus* MTCC-442	*C. albicans* MTCC-227	*A. niger* MTCC-282	*A. clavatus* MTCC-1323
7a	100	250	500	125	>1000	>1000	>1000
7b	62.5	200	500	500	500	>1000	>1000
7c	100	500	100	250	>1000	>1000	>1000
7d	125	250	200	200	1000	>1000	>1000
8a	100	100	250	100	500	1000	1000
8b	200	250	125	200	1000	1000	1000
8c	200	125	125	100	250	500	500
8d	250	200	200	250	200	500	500
9a	200	100	125	500	500	500	500
9b	500	125	62.5	125	500	>1000	>1000
9c	500	200	100	200	1000	>1000	>1000
9d	250	250	200	250	1000	>1000	>1000
Ampicillin	100	100	250	100	-	-	-
Griseofulvin	-	-	-		500	100	100

Acknowledgement

We are grateful to B. K. M. Science College, Valsad for providing research facilities, Atul Ltd. (Atul) for the IR spectral analysis and RSIC Punjab University for the ^{1}H NMR spectral analysis.

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