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An efficient synthesis of some novel isoxazoles, cyanopyridines and pyrimidinthiones

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ABSTRACT

*The title compounds **(7a-f)**, **(8a-f)** and **(9a-f)** have been prepared from chalcones **(6a-f)** 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-f)** and cyanopyridines **(8a-f)** respectively. Chalcones **(6a-f)** on condensation with thiourea in the presence of alkali give pyrimidinthiones **(9a-f)**. Structures of newly synthesised compounds were established on the basis of their elemental analysis, IR and ^{1}H NMR spectral data. Antibacterial activity (minimum inhibitory concentration MIC) against Gram-positive (S. aureus MTCC 96 and S. pyogeneus MTCC 442) and Gram-negative (P. aeruginosa MTCC 1688 and E. coli MTCC 443) bacteria, as well as antifungal acivity (MIC) against C. albicans MTCC 227, A. niger MTCC 282 and A. clavatus MTCC 1323 were determined by broth dilution method.*

Keywords Isoxazoles, Cyanopyridines, Pyrimidinethiones, Spectral data, Microbial studies.

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 antitubercular [4] etc. Pyridine derivatives have proven to be of great importance in exhibiting and enhancing the biological activities [5]. Substituted pyridine derivatives like cyanopyridines have found to possess different biological activities such as anticancer [6], antihypertensive [7] and arthropodicidal [8] etc. Pyrimidinethiones have been found to possess antiparasitic [9], antitumor [10] and hypoglycemic [11] etc… activities.

In a continuation of our work [12-15], the scope for further studies on chalcones and its derivatives, we herein report some novel isoxazoles **(7a-f)**, cyanopyridines **(8a-f)** and pyrimidinethiones **(9a-f)**. The synthesised compounds were ascertained from spectral and

physiochemical analysis. Results of IR and ^{1}H NMR analysis confirmed formation of the desired products.

MATERIALS AND METHODS

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 [16].

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

Compound **6a** (0.01 mol) was dissolved in ethyl alcohol (25ml) and hydroxylamine hydrochloride (0.01 mol) was added to it. Then the solution of KOH (5ml 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-f)** were prepared by this method.

Compound (7a) IR (KBr,cm^{-1}): 3405 (N-H str.), 3066 (=CH str.), 809 (C-N str., *s*-triazine moiety), 822 (C-H bending), 1625 (C=N str, isoxazole moiety), 1266 (C-O-C str.), 1095 (C-F str.) ; ^{1}H NMR ($CDCl_3$, δ, ppm): 3.81 (3H, *s*, m-OCH_3), 6.81 (1H, *s*, -CH=), 7.0 – 8.0 (17H, *m*, Ar-H and -NH).

Compound (7b) IR (KBr,cm^{-1}): 3408 (N-H str.), 3075 (=CH str.), 812 (C-N str, *s*-triazine moiety), 828 (C-H bending), 1640 (C=N str, isoxazole moiety) 1267 (C-O-C str), 1096 (C-F str) ; ^{1}H NMR ($CDCl_3$, δ, ppm): 3.80 (6H, *s*, m-OCH_3), 3.85 (3H, *s*, p-OCH_3), 6.70 (1H, *s*, -CH=), 7.1 – 8.1 (15H, *m*, Ar-H and -NH).

Compound (7c) IR (KBr,cm^{-1}): 3410 (N-H str.), 3080 (=CH str.), 816 (C-N str., *s*-triazine moiety), 835 (C-H bending), 1641 (C=N str, isoxazole moiety), 1270 (C-O-C str.), 1088 (C-F str.) ; ^{1}H NMR ($CDCl_3$, δ, ppm): 6.85 (1H, *s*, -CH=), 7.0 – 8.0 (22H, *m*, Ar-H and -NH).

Compound (7d) IR (KBr,cm^{-1}): 3407 (N-H str.), 3085 (=CH str.), 818 (C-N str, *s*-triazine moiety), 837 (C-H bending), 1644 (C=N str, isoxazole moiety), 1087 (C-F str.), 1545 (C-NO_2) ; ^{1}H NMR ($CDCl_3$, δ, ppm) : 6.81 (1H, *s*, -CH=), 7.0 – 8.0 (17H, *m*, Ar-H and -NH).

Compound (7e) IR (KBr,cm^{-1}): 3404 (N-H str.), 3089 (=CH str.), 816 (C-N str, *s*-triazine moiety), 835 (C-H bending), 1646 (C=N str, isoxazole moiety), 595 (C-Br str), 1088 (C-F str.) ; ^{1}H NMR ($CDCl_3$, δ, ppm): 6.82 (1H, *s*, -CH=), 7.2 – 8.2 (17H, *m*, Ar-H and -NH).

Compound (7f) IR (KBr,cm^{-1}): 3413 (N-H str.), 3074 (=CH str.), 818 (C-N str, *s*-triazine moiety), 835 (C-H bending), 1643 (C=N str, isoxazole moiety), 1271 (C-O-C str.), 1087 (C-F str.), 780(C-Cl str.); ^{1}H NMR ($CDCl_3$, δ, ppm): 6.84 (1H, *s*, -CH=), 7.1 – 8.1 (16H, *m*, Ar-H and -NH).

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

Compound **6a** (0.01 mol) was dissolved in ethyl alcohol (25ml) 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-f)** were prepared by this method.

Compound (8a) IR (KBr,cm^{-1}) : 3410 (N-H str.), 3062 (=CH str.), 809 (C-N str, *s*-triazine moiety), 1618 (C=N str, cyanopyridine moiety), 1095 (C-F str.) ; ^{1}H NMR ($CDCl_3$, δ, ppm) : 3.8 (3H, *s* , m-OCH_3), 6.8 (2H, *s*, -NH_2), 7.0 – 8.0 (18H, *m*, Ar-H and -NH).

Compound (8b) IR (KBr,cm^{-1}) : 3409 (N-H str.), 3065 (=CH str.), 811 (C-N str, *s*-triazine moiety), 1575 (C=N str., cyanopyridine moiety), 1090 (C-F str.) ; ^{1}H NMR ($CDCl_3$, δ, ppm) : 3.4 (6H, *s* , m-OCH_3), 3.6 (3H, *s*, p-OCH_3), 6.8 (2H, *s*, -NH_2), 7.0 – 8.0 (21H, *m*, Ar-H and -NH).

Compound (8c) IR (KBr,cm^{-1}) : 3405 (N-H str.), 3065 (=CH str.), 810 (C-N str, *s*-triazine moiety), 1585 (C=N str, cyanopyridine moiety), 1271 (C-O-C str.), 1097 (C-F str.) ; ^{1}H NMR ($CDCl_3$, δ, ppm) : 6.8 (2H, *s*, -NH_2), 7.0 – 8.0 (18H, *m*, Ar-H and -NH).

Compound (8d) IR (KBr,cm^{-1}) : 3407 (N-H str.), 3070 (=CH str.), 813 (C-N str, *s*-triazine moiety), 1580 (C=N str, cyanopyridine moiety), 1547 (C-NO_2), 1098 (C-F str.) ; ^{1}H NMR ($CDCl_3$, δ, ppm) : 6.9 (2H, *s*, -NH_2), 7.2 – 8.2 (18H, *m*, Ar-H and -NH).

Compound (8e) IR (KBr,cm^{-1}) : 3408 (N-H str.), 3072 (=CH str.), 812 (C-N str, *s*-triazine moiety), 1581 (C=N str, cyanopyridine moiety), 1098 (C-F str.), 595 (C-Br) ; ^{1}H NMR ($CDCl_3$, δ, ppm) : 6.8 (2H, *s*, -NH_2), 7.2 – 8.2 (18H, *m*, Ar-H and -NH).

Compound (8f) IR (KBr,cm^{-1}) : 3411 (N-H str.), 3069 (=CH str.), 811 (C-N str, *s*-triazine moiety), 1570 (C=N str, cyanopyridine moiety), 1096 (C-F str.); ^{1}H NMR ($CDCl_3$, δ, ppm) : 6.5 (2H, *s*, -NH_2) , 7.3 – 8.3 (17H, *m*, Ar-H and -NH).

Preparation of 2,4-bis-(2',4'-difluorophenylamino)-6-[4′-{2″- mercapto -6″-(3‴-methoxyphenyl) – pyrimidin - 4″-yl}phenylamino]-*s*-triazine (9a)

Compound **6a** (0.01 mol) was dissolved in ethyl alcohol (25ml) and thiourea (0.01 mol) was added to it. Then solution of KOH (5ml 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-f)** were prepared by this method.

Compound (9a) IR (KBr,cm^{-1}) : 3405 (N-H str.), 3065 (=CH str.), 809 (C-N str., *s*-triazine moiety), 825 (C-H bending), 1645 (C=N str, pyrimidine moiety), 1266 (C-O-C str.), 1095 (C-F str.) ; ^{1}H NMR ($CDCl_3$, δ, ppm) : 3.81 (3H, *s*, m-OCH_3), 11.1 (1H, *s*, -SH), 6.85 (1H, *s*, -CH=), 7.0 – 8.0 (17H, *m*, Ar-H and -NH).

Compound (9b) IR (KBr,cm^{-1}) : 3410 (N-H str.), 3070 (=CH str.), 810 (C-N str, *s*-triazine moiety), 830(C-H bending), 1642 (C=N str, pyrimidine moiety) 1267 (C-O-C str), 1098 (C-F str) ; ^{1}H NMR ($CDCl_3$, δ, ppm) : 3.4 (6H, *s* , m-OCH_3), 3.6 (3H, *s*, p-OCH_3), 11.2 (1H, *s*, -SH), 6.87 (1H, *s*, -CH=), 7.0 – 8.0 (15H, *m*, Ar-H and -NH).

Compound (9c) IR (KBr,cm^{-1}) : 3412 (N-H str.), 3072 (=CH str.), 812 (C-N str., *s*-triazine moiety), 832 (C-H bending), 1641 (C=N str, pyrimidine moiety), 1270 (C-O-C str.), 1098 (C-F str.) ; ^{1}H NMR ($CDCl_3$, δ, ppm) : 11.3 (1H, *s*, -SH), 6.83 (1H, *s*, -CH=), 7.0 – 8.0 (22H, *m*, Ar-H and -NH).

Compound (9d) IR (KBr,cm^{-1}) : 3410 (N-H str.), 3071 (=CH str.), 815 (C-N str, *s*-triazine moiety), 830 (C-H bending), 1644 (C=N str, pyrimidine moiety), 1555 (C- NO_2 str), 1087 (C-F str.); ^{1}H NMR ($CDCl_3$, δ, ppm) : 11.1 (1H, *s*, -SH), 6.81 (1H, *s*, -CH=), 7.0 – 8.0 (17H, *m*, Ar-H and -NH).

Compound (9e) IR (KBr,cm^{-1}) : 3410 (N-H str.), 3072 (=CH str.), 816 (C-N str, *s*-triazine moiety), 832 (C-H bending), 1646 (C=N str, pyrimidine moiety), 1087 (C-F str.), 591 (C- Br str) ; ^{1}H NMR ($CDCl_3$, δ, ppm) : 11.2 (1H, *s*, -SH), 6.82 (1H, *s*, -CH=), 7.1 – 8.1 (17H, *m*, Ar-H and -NH).

Compound (9f) IR (KBr,cm^{-1}) : 3413 (N-H str.), 3074 (=CH str.), 818 (C-N str, *s*-triazine moiety), 835 (C-H bending), 1643 (C=N str, pyrimidine moiety), 1271 (C-O-C str.), 1087 (C-F str.); ^{1}H NMR ($CDCl_3$, δ, ppm) : 11.3 (1H, *s*, -SH), 6.85 (1H, *s*, -CH=), 7.1 – 8.1 (16H, *m*, Ar-H and -NH).

RESULTS AND DISCUSSION

Minimum inhibitory concentration (MIC) of all the synthesised compounds have been screened by broth dilution method against four different strains, viz. Gram positive bacteria (*S. aureus* MTCC 96 and *S. pyogenes* MTCC 442) and Gram negative bacteria (*E. coli* MTCC 443 and *P. aeruginosa* MTCC 1688) and compared with standard drug : Ampicillin. Antifungal activity against *C. albicans* MTCC 227, *A. niger* MTCC 282 and *A. clavatus* MTCC 1323 organisms was determined by same method and compared with standard drug : Griseofulvin.

Antibacterial activity

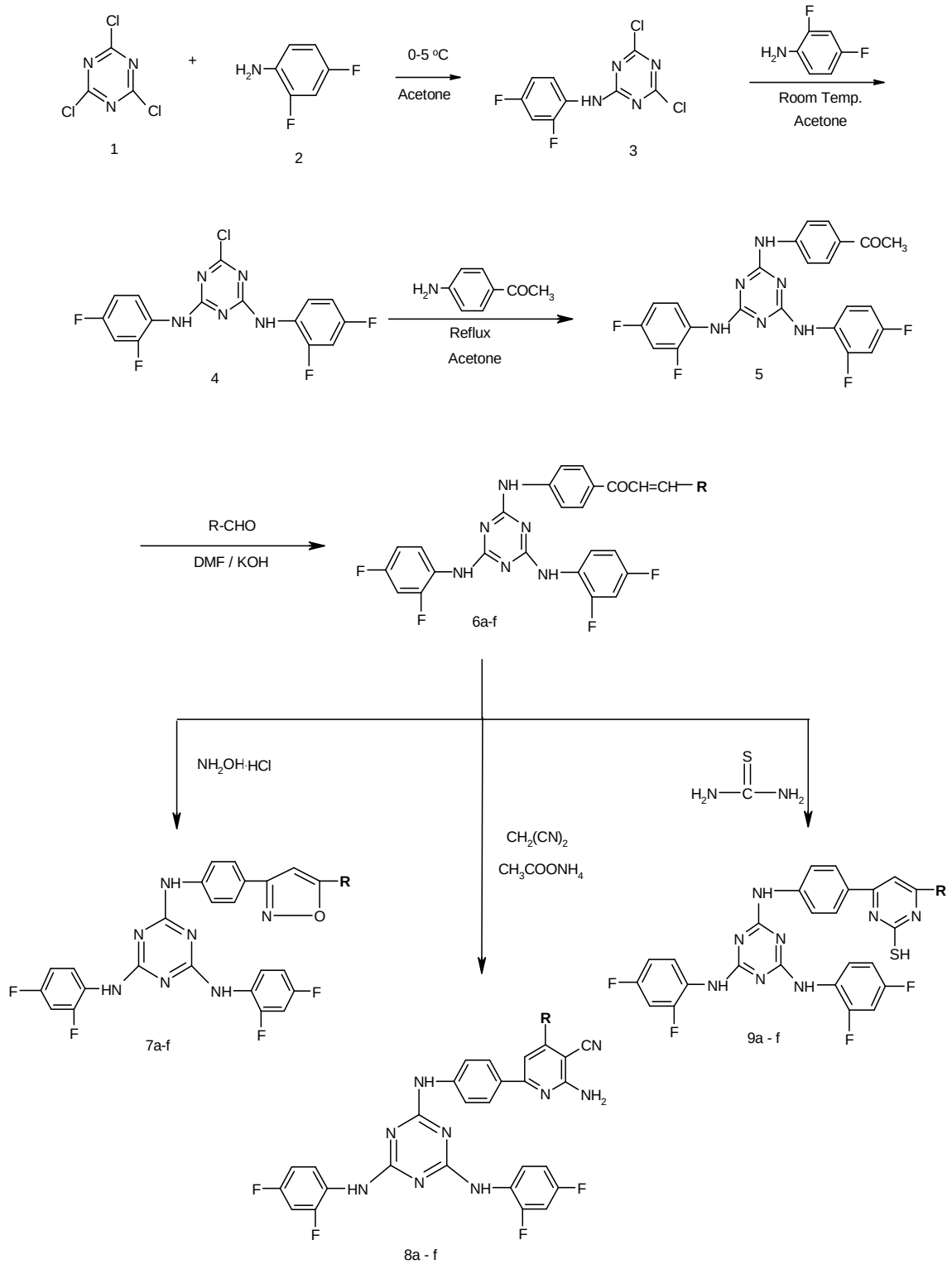
In Gram positive bacterial strains compounds **7a , 7d , 8c** and **9a** showed good to very good activity (25 – 150 µg/ml) against *S. aureus* ; where as compounds **7a** and **8c** showed good activity (62.5 – 100 µg/ml) against *S. pyogenes* compared with Ampicillin. In Gram negative bacterial strains,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

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

Compds	R	M. F	m.p °C	Elemental Analysis		
				% C Found (Calcd)	% N Found (Calcd)	% H Found (Calcd)
7a	3-Methoxyphenyl	$C_{31}H_{21}F_4N_7O_2$	115	62.07 (62.10)	16.33 (16.35)	3.51 (3.53)
7b	3,4,5-Trimethoxyphenyl	$C_{33}H_{25}F_4N_7O_4$	114	60.05 (60.09)	14.85 (14.86)	3.79 (3.82)
7c	3-Phenoxyphenyl	$C_{36}H_{23}F_4N_7O_2$	110	65.33 (65.35)	14.81 (14.82)	3.48 (3.50)
7d	3-Nitrophenyl	$C_{30}H_{18}F_4N_8O_3$	195	58.60 (58.64)	18.22 (18.23)	2.93 (2.95)
7e	3-Bromophenyl	$C_{30}H_{18}BrF_4N_7O$	120	55.54 (55.57)	15.10 (15.12)	2.77 (2.80)
7f	2-Furanyl	$C_{28}H_{17}F_4N_7O_2$	165	60.10 (60.11)	17.49 (17.52)	3.03 (3.06)
8a	3-Methoxyphenyl	$C_{34}H_{23}F_4N_9O$	105	62.85 (62.86)	19.37 (19.41)	3.53 (3.57)
8b	3,4,5-Trimethoxyphenyl	$C_{36}H_{27}F_4N_9O_3$	113	60.90 (60.93)	17.68 (17.76)	3.80 (3.83)
8c	3-Phenoxyphenyl	$C_{39}H_{25}F_4N_9O$	106	65.80 (65.82)	17.69 (17.71)	3.52 (3.54
8d	3-Nitrophenyl	$C_{33}H_{20}F_4N_{10}O_2$	118	59.59 (59.62)	21.06 (21.08)	3.02 (3.03)
8e	3-Bromophenyl	$C_{33}H_{20}BrF_4N_9$	117	56.71 (56.75)	18.01 (18.05)	2.85 (2.89)
8f	2-Furanyl	$C_{31}H_{19}F_4N_9O$	113	61.04 (61.09)	20.64 (20.68)	3.12 (3.14)
9a	3-Methoxyphenyl	$C_{32}H_{22}F_4N_8OS$	110	59.79 (59.81)	17.40 (17.44)	3.44 (3.45)
9b	3,4,5-Trimethoxyphenyl	$C_{34}H_{26}F_4N_8O_3S$	106	58.10 (58.12)	15.91 (15.95)	3.70 (3.73)
9c	3-Phenoxyphenyl	$C_{37}H_{24}F_4N_8OS$	95	63.02 (63.06)	15.86 (15.90)	3.40 (3.43)
9d	3-Nitrophenyl	$C_{31}H_{19}F_4N_9O_2S$	220	56.59 (56.62)	19.15 (19.17)	2.85 (2.91)
9e	3-Bromophenyl	$C_{31}H_{19}BrF_4N_8S$	113	53.83 (53.85)	16.18 (16.20)	2.75 (2.77)
9f	2-Furanyl	$C_{29}H_{18}F_4N_8OS$	125	57.79 (57.81)	18.58 (18.60)	2.95 (3.01)

Antifungal activity

From the screening results **(Table – 2)**, compounds **7c** and **8d** showed very good activity against *C. albicans*, while Compounds **7d , 7f , 8c , 8f , 9d** and **9f** showed good activity against *C. albicans* compared with Griseofulvin. Rest of the compounds show moderately active or less active against all bacterial strains.


0-5 °C
Acetone
Room Temp.
Acetone
Reflux
Acetone
R-CHO
DMF / KOH
NH2OH·HCl
CH2(CN)2
CH3COONH4
1
2
3
4
5
6a-f
7a-f
9a - f
8a - f

SCHEME -1

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	250	500	100	100	>1000	500	500
7b	125	200	200	200	1000	>1000	>1000
7c	200	500	200	200	250	>1000	>1000
7d	200	250	100	125	500	>1000	>1000
7e	125	200	200	250	>1000	500	500
7f	100	100	250	200	500	>1000	>1000
8a	200	100	500	200	>1000	>1000	>1000
8b	125	200	200	200	1000	500	1000
8c	250	125	62.5	100	500	500	500
8d	125	200	200	200	250	>1000	>1000
8e	250	125	250	250	1000	500	500
8f	250	500	200	250	500	>1000	>1000
9a	500	125	62.5	125	>1000	>1000	>1000
9b	200	200	200	500	500	1000	1000
9c	250	250	200	250	>1000	>1000	>1000
9d	100	500	250	250	500	>1000	>1000
9e	100	250	250	250	1000	>1000	>1000
9f	50	100	500	500	500	1000	1000
Ampicillin	100	100	250	100	-	-	-
Griseofulvin	-	-	-		500	100	100

CONCLUSION

From the results of antibacterial and antifungal activity; it can be concluded that the compounds bearing methoxy , phenoxy and furanyl group are more potent than the remaining compounds. They showed comparatively good antibacterial as well as antifungal activity.

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