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Potential antibacterial agents: Phenylpyrazolines, cyanopyridines and isoxazoles

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ABSTRACT

*A series of 2-(4'-chloro phenyl amino)-4-(4'-fluoro phenyl amino)-6-[4'-{1''-phenyl-5''-substitutedphenyl-2''-pyrazolin-3''-yl}phenylamino]-s-triazine **(7a-e)**, 2-(4'-chlorophenylamino)-4-(4'-fluorophenylamino)-6-[4'-{2''-amino-3''-cyano-4''-substitutedphenyl-pyridin-6''-yl}phenylamino]-s-triazine **(8a-e)** and 2-(4'-chloro phenyl amino)-4-(4'-fluoro phenyl amino)-6-[4'-{5''-substituted phenyl-isoxazole-3''-yl}phenylamino]-s-triazine **(9a-e)** were prepared. The structures of synthesized were confirmed on the basis of spectral data. The compounds were screened for their in vitro antibacterial activity using Gram-positive and Gram-negative bacteria.*

Keywords: Phenylpyrazolines, Cyanopyridines, Isoxazoles, Spectral data, Antibacterial activity.

INTRODUCTION

Synthesis and characterization of pyrazoline derivatives has been developing field in the realm of heterocyclic chemistry for the past several decads due to their wide range of biological activities such as anticancer [1], anticonvulsant [2], antibacterial [3] etc. Substituted pyridine derivatives like cyanopyridine have been found to possess analgesic [4], antiproferative [5] and antifungal [6] activities. Isoxazoles have found to be effective as antimicrobial [7], anti–inflammatory [8] and antiprotozoal [9] agents. In view of this and in continuation of our work [10-12] on synthetic heterocycles, we herein report the synthesis of phenylpyrazolines **(7a-e),** cyanopyridines **(8a-e)** and Isoxazoles **(9a-e).** All the synthesized compounds were established on the basis of their spectral data and physical data. These compounds were screened for their antibacterial activity.

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 part 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 : actone (10 : 4 v/v) and visualized with UV (254nm) 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 [13].

Preparation of 2-(4'-chlorophenylamino)-4-(4'-fluorophenylamino)-6-[4'-{1''-phenyl-5''-(3'''-methoxyphenyl)-2''-pyrazolin-3''-yl} phenylamino]-*s*-triazine (7a):
2-(4'-Chloro phenyl amino)-4-(4'-fluoro phenyl amino)-6-[4'-{3"-(3'"-methoxy phenyl)-2"-propenon-1"-yl}phenyl amino]-*s*-triazine **6a** (0.01 mole) and phenyl hydrazine hydrochloride (0.01mole) in alcohol (30 ml) was added to it. Then solution of 40% KOH (8 ml) was added to the reaction mixture and refluxe for 12 hours. The progress of reaction was monitored on TLC plate. After compilation, the reaction mixture was then cooled, poured into crushed ice and neutralized with diluted HCL. The product separated out was filtered, washed with water, dried and recrystallized from alcohol to give **7a**.

Similarly the remaining compounds **(7b-e)** were prepared by this method. Their molecular formula, melting point and analytical data are shown in **Table I**

Compound (7a) Yield 65%, m.p 105°C. (IR , KBr, cm^{-1}) : =CH str. (3050),1580 (C=N str), 1037 (C-O-C), 1018 (C-F str.), 809 (C-N, *s* –triazine), 740 (C-Cl str.), ^{1}H NMR (DMSO, δ , ppm) : 3.1 (1H, *dd*, $-CH_{2\ pyraz}$), 3.3 (1H, *dd*, $-CH_{2\ pyraz}$), 3.88 (3H, *s*, m-OCH_3), 3.74 (1H, *dd*, -CH), 6.9-7.81 (24H, *m*, Ar-H+NH). Anal, Calcd. For $C_{37}H_{30}ClFN_8O$: C, 67.63; H,4.56 ; N, 17.03. Found: C, 67.66; H,4.52; N, 17.01%.

Preparation of 2-(4'-chlorophenylamino)-4-(4'-fluorophenylamino)-6-[4'-{2"-amino-3"-cyano-4"-(3'''-methoxyphenyl)-pyridine-6"-yl} phenylamino]-s-triazine (8a):
Compound **6a** (0.01 mole) was dissolved in alcohol (25ml), malanonitrile (0.01 mole) and ammonium acetate (0.08 mole) was added to it and refluxed for 8 hours. The progress of reaction was monitored on TLC plate. The reaction mixture was then cooled, poured into crushed ice and product separated out was filtered, washed with water, dried and recrystallized from alcohol to give **8a**

Remaining compounds **(8b-e)** were synthesized by the same procedure and their molecular formula, melting point and analytical data are shown in **Table I**

Compound (8a) Yield 68%, m.p 96°C. (IR, KBr, cm^{-1}) : 3468 ($-NH_2$), 2207 (C≡N), 1230(C-O-C). 1013 (C-F), 803 (C-N, *s*-triazine), 780 (C-Cl); ^{1}H NMR (DMSO, δ, ppm) : 3.82 (3H, s, m-OCH_3), 6.9 (2H, s, $-NH_2$), 7.2 to 8.4 (20H, m, Ar-H +NH). Anal, Calcd. For $C_{34}H_{25}ClFN_9O$: C, 64.81; H,3.97; N, 20.01. Found: C, 64.76; H, 3.93 ; N, 20.08%.

Preparation of 2-(4'-chloro phenyl amino)-4-(4'-fluoro phenyl amino)-6-[4'-{5''-(3'''- methoxy phenyl)-isoxazole-3''-yl}phenylamino]-s-triazine (9a):
Compound **6a** (0.01 mole) was dissolved in alcohol (25ml) and hydroxylamine hydrochloride (0.01mole) was added to it. Then solution of KOH was added to the reaction mixture and refluxed for 6 hours. The progress of reaction was monitored on TLC plate. The reaction mixture was then cooled, poured into crushed ice and product separated out was filtered, washed with water, dried and recrystallized from alcohol to give **9a**.

Remaining compounds **(9b-e)** were synthesized by the same procedure and their molecular formula, melting point and analytical data are shown in **Table I**

Compound (9a) Yield 70%, m.p 160°C. (IR , KBr, cm^{-1}) : 1575 (C=N, isoxazole moiety), 1012 (C-F), 805 (C-N, *s*-triazine), 785 (C-Cl)];); ^{1}H NMR (DMSO, δ, ppm) : 3.80 (3H, s, m-OCH_3), 6.90 (lH,s,-CH of isoxazolemoiety), 7.0–8.0(19H, m, Ar-H+NH). Anal, Calcd. For $C_{31}H_{23}ClFN_7O_2$: C, 64.19; H,3.96; N, 16.91 . Found: C, 64.22; H,3.92; N, 16.85%.

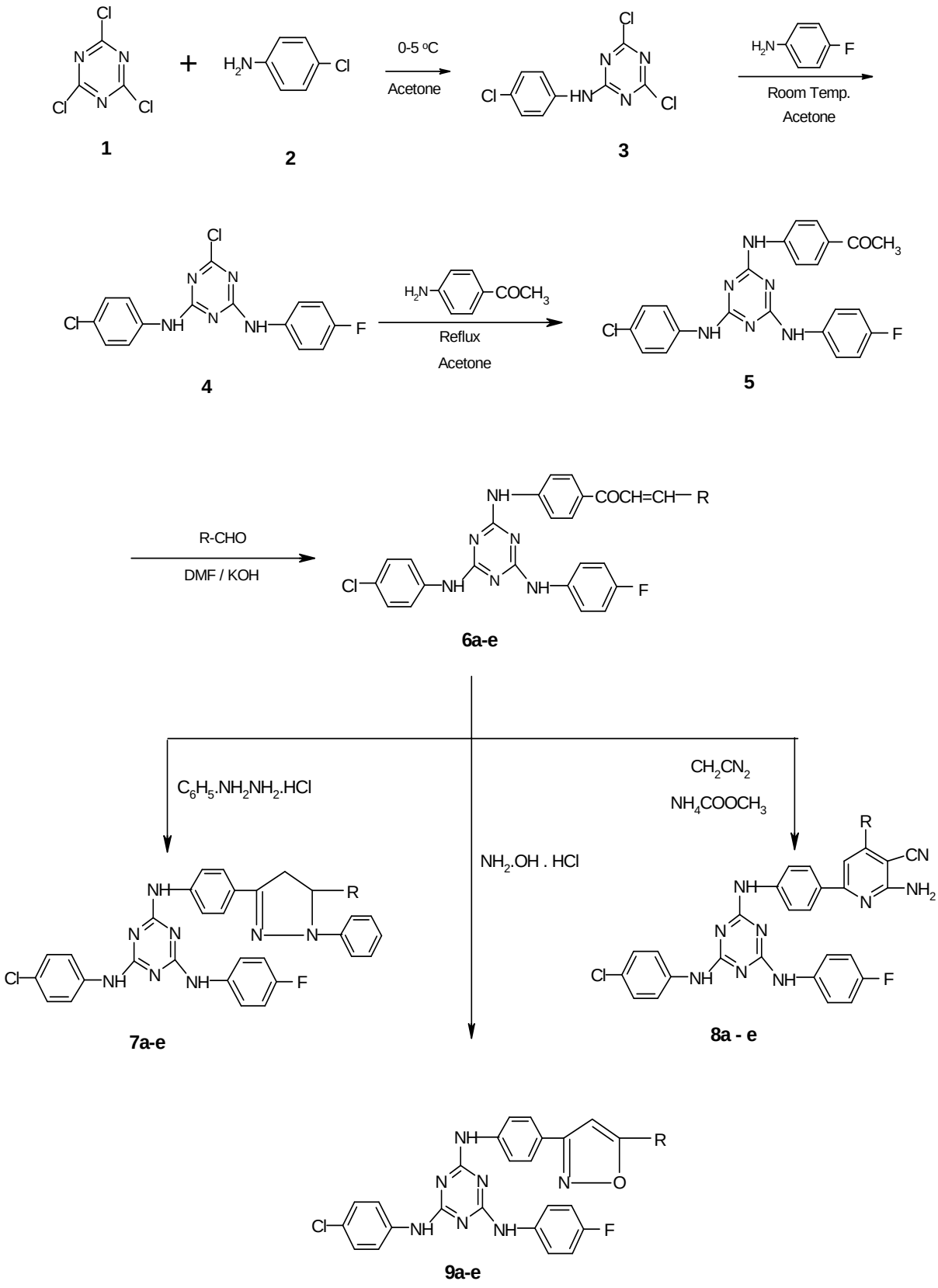
Table -I Characterization data of compounds (7a-e), (8a-e) and (9a-e)

Compd	R	M. F	m.p °C	Elemental Analysis		
				% C Found (Calcd)	% N Found (Calcd)	% H Found (Calcd)
7a	3-Methoxyphenyl	$C_{37}H_{30}ClFN_8O$	105	67.66 (67.63)	17.03 (17.06)	4.52 (4.56)
7b	4-Methoxyphenyl	$C_{37}H_{30}ClFN_8O$	110	67.69 (67.63)	17.08 (17.03)	4.59 (4.56)
7c	3-Phenoxyphenyl	$C_{42}H_{32}ClFN_8O$	112	70.19 (70.14)	15.53 (15.58)	4.40 (4.45)
7d	2-Nitrophenyl	$C_{36}H_{27}ClFN_9O_2$	80	64.36 (64.33)	18.72 (18.76)	4.04 (4.02)
7e	3-Nitrophenyl	$C_{36}H_{27}ClFN_9O_2$	86	64.37 (64.33)	18.73 (18.76)	4.06 (4.02)
8a	3-Methoxyphenyl	$C_{34}H_{25}ClFN_9O$	96	64.78 (64.81)	19.99 (20.03)	3.94 (3.97)
8b	4-Methoxyphenyl	$C_{34}H_{25}ClFN_9O$	140	64.85 (64.81)	19.98 (20.03)	3.93 (3.97)
8c	3-Phenoxyphenyl	$C_{39}H_{27}ClFN_9O$	105	67.64 (67.67)	18.18 (18.22)	3.86 (3.90)
8d	2-Nitrophenyl	$C_{33}H_{22}ClFN_{10}O_2$	140	61.40 (61.44)	21.77 (21.72)	3.37 (3.41)
8e	3-Nitrophenyl	$C_{33}H_{22}ClFN_{10}O_2$	195	61.39 (61.44)	21.74 (21.72)	3.38 (3.41)
9a	3-Methoxyphenyl	$C_{31}H_{23}ClFN_7O_2$	160	64.19 (64.21)	16.87 (16.91)	3.92 (3.96)
9b	4-Methoxyphenyl	$C_{31}H_{23}ClFN_7O_2$	250	64.18 (64.21)	16.86 (16.91)	3.93 (3.96)
9c	3-Phenoxyphenyl	$C_{36}H_{25}ClFN_7O_2$	170	67.38 (67.34)	15.31 (15.30)	3.84 (3.89)
9d	2-Nitrophenyl	$C_{30}H_{20}ClFN_8O_3$	160	60.51 (60.55)	18.79 (18.83)	3.33 (3.36)
9e	3-Nitrophenyl	$C_{30}H_{20}ClFN_8O_3$	172	60.52 (60.55)	18.78 (18.83)	3.40 (3.36)

RESULTS AND DISCUSSION

Antibacterial activity

The antibacterial activity of the synthesized compounds have been assayed against *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 using agar diffusion method of A. L. Barry [14]. Known antibiotic like ciprofloxacin used for comparison **(Table-II).** Antibacterial activity data of the tested compounds revealed that compounds **7b, 9a and 9b** were found to be active against *S. aureus* (MTCC 96).


1
2
0-5 °C
Acetone
3
Room Temp.
Acetone
4
Reflux
Acetone
5
R-CHO
DMF / KOH
6a-e
C6H5.NH2NH2.HCl
NH2.OH . HCl
CH2CN2
NH4COOCH3
7a-e
8a - e
9a-e

SCHEME -1

Compounds **7a** ,**7d and 8a** were found to be moderately active against *S. aureus* (MTCC 96); where as reamaning compounds were found to be less or inactive against *S. aureus* (MTCC 96). Compounds **7d**, **7e**, **8c** and **9b** were found to be active against *B. subtilis* (MTCC 441). Compound **7c**, **8b**, **8e**, **9a** were found to be moderately active against *B. subtilis* (MTCC 441) where as reamaning compounds were found to be less or inactive against *B. subtilis* (MTCC 441). Compounds **7a**, **7b**, **7c**, **7d**, **7e, 8a**, **8b**, **8c**, **8d**, **8e, 9a**, **9b**, **9c**, **9d** and **9e** were found to be moderately active against *E. coli* (MTCC 443). Compounds **7b**, **7d**, **7e**, **8d** and **9c** were found to be active against *S. paratyphi-B* (MTCC 733). Compounds **7a**, **7c**, **8a**, **8b**, **8c**, **8e**, **9a**, **9b**, **9d** and **9e** were found to be moderately active against *S. paratyphi-B* (MTCC 733).

Table -II Antibacterial activity of compounds (7a-e), (8a-e) and (9a-e)

Compd	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	3-Methoxyphenyl	15	-	16	18
7b	4-Methoxyphenyl	18	10	17	21
7c	3-Phenoxyphenyl	-	15	15	19
7d	2-Nitrophenyl	17	18	17	20
7e	3-Nitrophenyl	10	19	17	20
8a	3-Methoxyphenyl	15	13	18	18
8b	4-Methoxyphenyl	-	15	15	19
8c	3-Phenoxyphenyl	12	18	16	16
8d	2-Nitrophenyl	-	-	16	20
8e	3-Nitrophenyl	12	17	15	18
9a	3-Methoxyphenyl	19	17	15	17
9b	4-Methoxyphenyl	19	19	18	19
9c	3-Phenoxyphenyl	-	-	17	20
9d	2-Nitrophenyl	-	12	17	17
9e	3-Nitrophenyl	-	11	18	19

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