RESEARCH ARTICLE Am. J. PharmTech Res. 2017; 7(1) ISSN: 2249-3387

AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Synthesis, Characterization and Antimicrobial Activities of Some Novel 2-Azetidinones Derived from Cyanoethyl Tertiaryamino Benzaldehydes

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ABSTRACT

Present report is the successful synthesis, spectral characterization and *in-vitro* antimicrobial evaluation of a series of azomethine and novel 2-azetidinone derivatives. Two cyanoethylated tertiaryaminobezaldehydes **A** and **B** were prepared by cyanoethylation of the corresponding aromatic primary amines followed by formylation in presence of $POCl_3$ and DMF. These cyanoethylated tertiaryaminobenzaldehydes on condensation with different aromatic primary amines afforded azomethines **SB**1-**SB**14, which on cyclization with chloroacetylchloride and triethylamines in 1,4-dioxan gave new 2-azetidinone **BL**1-**BL**14. All compounds were prepared by reported methodology and characterized by elemental analysis, FT-IR and ^{1}HNMR data. Further screened *in-vitro* for antimicrobial activity against *S. aureus, B. subtilis, P. vulgaris, E. coli, A. niger* and *A. fumigatus*. Most of the compounds showed significant activity against tested pathogens. The work shows the emergence of a new series of compounds in the field of antimicrobials.

Keywords: 2-Azetidinones, azomethines, antimicrobial activity, cyanoethylation, formylation, tertiaryaminobenzaldehydes.

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Received 12 December 2016, Accepted 27 December 2016

Please cite this article as: Soni PK *et al.*, Synthesis, Characterization and Antimicrobial Activities of Some Novel 2-Azetidinones Derived from Cyanoethyl Tertiaryamino Benzaldehydes. American Journal of PharmTech Research 2017.

INTRODUCTION

Antimicrobial drugs has saved millions of lives and eased the suffering of patients of all ages for more than 70 years. These “wonder drugs” deserve much of the credit for the dramatic increase in life expectancy around the world in the 20th century. The design of drug molecules arguably offers some of the greatest hopes for success in present and future era[1]. The treatment of infectious diseases is still an important and challenging problem due to the emergence of numerous infectious diseases and multi-drug resistant microbial pathogens. Resistant infections are difficult to treat, tend to spread relatively rapidly and increase healthcare costs significantly[2]. Antimicrobial resistance is one of the greatest growing challenges to global public health today. Some previously treatable pathogens are now becoming untreatable, for example *methicillin-resistant Staphylococcus aureus* (MRSA) and *vancomycin-resistant enterococcus*[3] (VRE). To overcome the alarming problem of microbial resistance to antibiotics, the discovery of novel compounds active against new targets is a matter of urgency. Now a day's pharmaceutical industries are looking for synthesizing the alternative compounds which can act as drug. It is well known that the introduction of fluorine atom on organic molecule causes dramatic changes in its biological properties[4-6].

Azomethines and their derivatives revealed a great promise in the area of synthesis and medical fields[7] and has been a research subject[8,9] due to their pharmacological applications and striking complexometric behaviour. These also play a pivotal role in various biological activities[10-15]anticancer[16-19], anticonvulsant[20,21], anti-HIV[22], anti-inflammatry[23], antimalarial[24,25], pesticidal[26] and herbicidal[27] activities. Tertiaryaminobenzaldehydes have been found of significant important on account of their role in the synthesis of chemotherapeutics[28,29] and analytical reagents[30].

The β-lactams also called 2-azetidinones are still the most prescribed antibiotics in medicine. These are considered as an important contribution of science to humanity[31]. The biological activity of antibiotics such as penicillins, cephalosporins and carbapenems is due to the presence of 2-azetidinone nucleus in them. The four-membered cyclic 2-azetidinone skeleton has been recognized as a useful building block for the synthesis of a large number of organic molecules. Many compounds containing cyanoethyl group have shown significant anticancer activity[32,33]. Azomethines formed by 4-N’N-bis-(2'-cyanoethyl)aminobenzalde hyde have been reported by Arora[34] *et al.* to prepare stable complexes with metals. A new series of complexes of dioxo-uranium (IV) with the azomethines N-[(4-N’N-bis-(2’cyanoethylaminobenzylidene-amino]benzene derived from N-[(4-N’N-bis-(2’cyanoethy lamino-benzy lideneamino]benzaldehyde and aniline were prepared by Arora[35] *et al*. Azomethines containing chloro and cyano group display enhanced antibacterial effects[36,37].

Efforts have been made in exploring such biological potential of azomethines and 2-azetidinones derived from cyanoethyltertiaryaminobezaldehydes for the synthesis and biological activity of 2-azetidinones incorporated with cyanoethyl moiety, halogen and cyano groups. There has been an increasing prevalence over the past decades in different biologically active compounds containing an acrylonitrile moiety[38-41]. Many compounds containing cyanoethyl group have shown significant anticancer activities[42,43]. Konkova and co-workers reported the formation of 2-aryl-3-cyano ethyltetrahydro-1,3-oxazines and 2-aryl-3-cyanoethyl-1,3-oxazolidines[44,45]

MATERIALS AND METHOD

Melting points were determined in an open capillary tube and are uncorrected. The chemicals and solvents used were of laboratory grade and purified further. Completion of the reaction was monitored by thin layer chromatography on pre-coated sheets of 25 DC alufolin Kieselgel 60 F_{254} silica gel 60 F_{254} (Merck) using UV-vis florescence analysis chamber for detection. FT-IR spectra were recorded in KBr on a Perkin-Elmer spectrophotometer-2. ^{1}H NMR spectra were recorded in DMSO-d6 with an advanced spectrophotometer (Bruker) at 400-MHz frequency using TMS as an internal standard and DMSO-*d6* as a solvent. Elemental analyses were performed on a Perkin-Elmer-240 elemental analyzer. All the synthesized compounds were purified by recrystellization in ethanol.

Preparation of 4-N’N-bis-2’-cyanoethylaminobenzaldehyde A:

I. Cyanoethylation of aniline; Formation of N’N-bis-2’-cyanoethyl aniline:

Freshly distilled aniline (17.65 mL, 0.193 mol), acrylonitrile (32.71 mL, 0.5 mol) and glacial acetic acid (23.809 mL) were gently refluxed for twelve hours. The brown liquid was cooled and poured with stirring into liquor ammonia (100 mL) the contents were left overnight; the solid separated was washed with water till free from copper salts and filtered under suction. The solid was dried and recrystellized from ethanol when N’N-bis-2’-cyanoethylaniline was obtained as colourless shining needles.

II. Formylation of N’N-bis-2’-cyanoethylaniline; Formation of 4-N’N-bis 2-cyano ethylaminobenzaldehyde: N’N-bis-2’-cyanoethyl aniline (13.8 g, 0.07 mol) was slowly added in small portion to a cold mixture of phosphorousoxychloride (6.808 mL, 0.07 mol) and dimethylformamide (19.40 mL, 0.25 mol), taken in a round bottomed flask provided with a mechanical stirrer and reflux condenser carrying a calcium chloride guard tube. The contents were heated on a steam bath for three hours while the mixture was stirred. After cooling, the dark brown liquid was poured over crushed ice and the clear solution neutralised by the addition of sodium acetate on keeping over night the solid product precipitated out. It was filtered under suction, washed with water and recrystellized from ethanol when the aldehyde was obtained as shining needles.

Preparation of 2-methyl-4-N'N-bis-cyanoethylaminobenzaldehyde B:

I. Cyanoethylation of *m*-toluidine; Formation of N'N-bis-2'cyanoethyl *m*-toluidine:

Freshly distilled *m*-toluidine (10.10 mL, 0.1 mol) acrylonitrile (13.43 mL, 0.25 mol), glacial acetic acid (13.33 mL, 0.25 mol) and freshly prepared dry cuprous chloride (1.0 g) were gently refluxed for twelve hours. The brown liquid was cooled and poured into liquor ammonia (100 ml). The contents were left overnight when the solid separated it was filtered under suction, washed well with water till free from copper salts. The solid was dried and recrystellized from ethanol in colourless needles.

II. Formylation of N'N-bis-2-cyanoethyl-*m*-toluidine; Formation of 2-methyl-4-N'N-bis-2'-cyanoethylaminobenzaldehyde:

N'N-bis-2-cyanoethyl-*m*-toluidine (11.6 g, 0.05 mol) was slowly added with stirring to cooled mixture of phosphorous oxychloride (5.47 mL, 0.05 mol) and dimethylformamide (16.64 mL, 0.2 mol) taken in a round bottomed flask provided with a mechanical stirrer and a Liebig's condenser, carrying calcium chloride guard tube. The contents were heated with stirring on a steam bath for three hours. The dark brown liquid was cooled, poured over crushed ice and the clear solution was neutralised with sodium acetate on keeping overnight the solid product separated, it was filtered under suction, washed well with water till free from copper salts. The solid was dried and recrystellized from ethanol, the aldehyde was obtained as light yellow needles.

General procedure for the preparation of Azomethines SB1**-SB**14**:**

A mixture of equimolar amount (0.01mol) of aromatic aldehydes and aniline or *o*-, *m*-, *p*-fluoro/chloro aromatic amines in ethanol (20mL) and concentrated sulphuric acid (2-3 drops) was refluxed for 6-8 hrs at 60-80^{0}C. Progress of reaction was measured by TLC. The reaction mixture was concentrated and cooled at room temperature and kept overnight and transferred into crushed ice with addition of 1-2 drops of concentrated sulphuric acid. The solid obtained was filtered by washing two times with distilled water followed by drying into air and recrystellized with ethanol to give azomethines as yellow crystals. Yield of compounds were found between 52.02-63.56%. The characterization data has confirmed the formation of required compounds.

General procedure for the preparation of 2-Azetidinones BL1**-BL**14**:**

A mixture of azomethines **SB**1-**SB**14 (0.01mol) and triethylamine (0.01 mol) was dissolved in 1,4-dioxane (50 mL) was stirred and cooled. Chloroacetylchloride (0.01 mol) was added drop wise within a period of 30 minutes. The reaction mixture was stirred further for 8-12 hours at 50-80^{0}C with monitoring the progress of reaction by TLC. The reaction mixture was concentrated, cooled and poured into crushed ice and water, after one hour solid precipitate was filtered and washed with water and then air dried. The product thus obtained was recrystellized using ethanol. 2-azetidinones obtained with dark coloured crystals. Yield of compounds were found between 65.42-44.61%. Formation of product was confirmed by characterization data.

(i) Analytical data of 3,3'-((4-formyl-3-methyl phenyl)azanediyl)dipropanenitrile B:

Molecular Formula: $C_{14}H_{15}N_3O$; Yields; 61.12, m.p. 97^{0}C.

Elements % (Required) Found: C (69.69) 68.80, H (6.27) 5.85 N (17.41) 17.30.

FT-IR absorption frequencies in KBr (cm^{-1}); C=O (1676.5), N-CH_2 (2247.7), CH_2CN (2745.2) CH_3 (1599.5), CH-Ar (2971.8). **^{1}H NMR** in DMSO-d_6 (δ ppm); CH_3 (3HS) 2.508, CH_2CN (4HT) 2.795-2.829, CH_2CH_2CN (4HT) 3.814-3.848, Ar (1HD) 6.996-7.018, Ar (1HS) 7.216, Ar (1HD) 7.717-7.739, CHO (1HS) 9.734.

(ii) Analytical data of (Z)-3,3'-((4-(((4-chlorophenyl)imino)methyl)-3-methylphenyl) azanediyl)dipropanenitrile (Azometnine SB14**):**

Molecular Formula: $C_{22}H_{20}Cl_2N_4O$; Yields; 52.09, m.p. 98^{0}C.

Elements % (Required) Found: C (68.47) 67.95, H (5.46) 5.43, N (15.97) 15.41.

FT-IR absorption frequencies in KBr (cm^{-1}); C=O (1679.6), N-CH_2 (2249.1), CH_2-CN (2744.2), CH_3 (1626.2), CH-Ar (2973.6). **^{1}H NMR** in DMSO-d_6 (δ ppm): CH_3 (3HS) 2.512-2.563, CH_2CN (4HT) 2.781-2.816, CH_2CH_2CN (4HT) 3.795-3.829, Ar (1HS) 6.752, Ar (1HD) 6.758-6.822, Ar (2HD) 7.628-7.650, Ar (3HD_3) 8.754-8.853, CH=N (1H) 9.935.

(iii) Analytical data of 3,3'-((4-(3-chloro-1-(4-chlorophenyl)-4-oxoazetidin-2-yl)-3-methyl phenyl)azanediyl)dipropanenitrile (2-azetidinone BL14**):**

Molecular Formula: $C_{22}H_{20}ClFN_4O_{2;}$ Yields; 54.46, m.p. 102^{0}C.

Elements % (Required) Found: C (61.83) 61.52 H (4.72) 4.51, N (13.11) 13.04

FT-IR absorption frequencies in KBr (cm^{-1}); C=O (1749.2), CH_3 (1630.4), CH_2-C-CN (2249.1), CH_2CN (2039.9), CH-Ar (2981.7). **^{1}H NMR** in DMSO-d_6 (δ ppm): CH_2CN (4HT) 3.210-3.342, CH_2CH_2CN (4HT) 3.718-3.795, CH_3 (3HS) 2.326, CH of 2-azetidinone Ring (1HD) 5.232-5.253, CHCl of 2-azetidinone Ring (1HD) 5.631-5.659, Ar (1HS) 6.379, Ar (1HD) 6.479-6.483, Ar (1HD) 7.531-7.553, Ar (1HD) 8.689, Ar (1HD) 8.747, Ar (1HT) 8.884, Ar (1HT) 8.921.

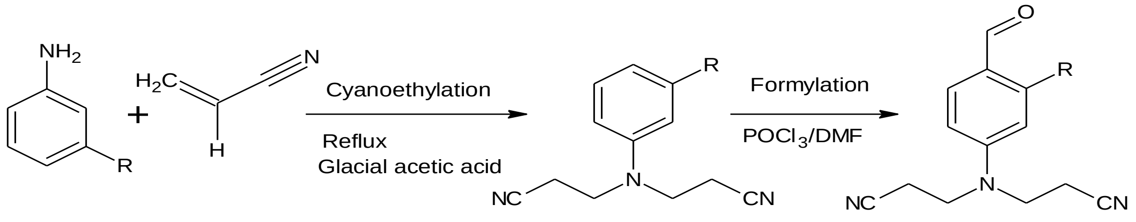
The *in-vitro* antimicrobial susceptibility testing of synthesized compounds

All the synthesized azomethines **SB1-**14 and 2-azetidinones **BL1-**14 were subjected to *in-vitro* antimicrobial susceptibility testing against bacterial and fungal strains in order to determine their efficacy and structure-activity relationship taking Ampicillin as broad-spectrum antibacterial and Fluconazole as antifungal standard drugs. The antimicrobial activities of the synthesized compounds were studied by disc diffusion method. The serial dilution method was used to determine the minimum inhibitory concentration (MIC) of the synthesized compounds. DMSO was used as the negative control solvent for the compounds. Few colonies of organisms in 2-5 mL nutrient Mueller-Hinton agar medium (for bacteria strainsl) and Sabourauds broth (for fungal strains) were grown for 2.5 h. After the inoculums dried, 6 mm diameter wells were made in the agar plate with a sterile cork borer. The synthesized compounds were dissolved in DMF at concentrations of 300μg and 600μg/mL. The Petri plates were incubated at 37ºC for 24 hours. The Zone of inhibition was measured in mm to estimate the potency of the test compounds.

RESULTS AND DISCUSSION

Synthesis of cyanoethyltertiaryaminobezaldehydes:

Two cyanoethyltertiaryaminobezaldehydes **A** and **B** were synthesized (Scheme-**1)** by the cyanoethylation of the corresponding aromatic primary amines by acrylonitrile and glacial acetic acid followed by formylation in presence of $POCl_3$ and DMF.

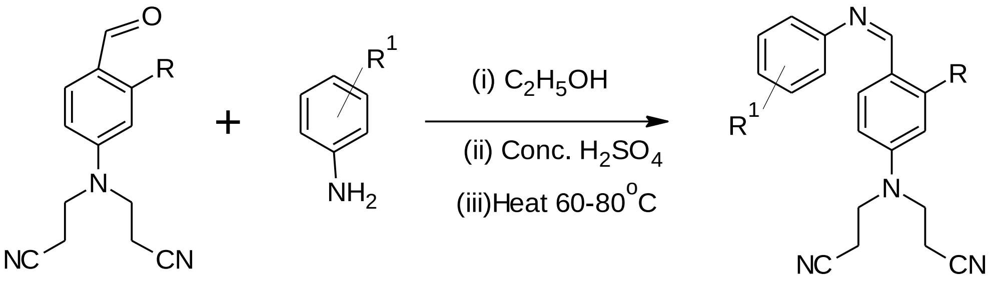


R = -H (**A**), $-CH_3$ (**B**)

Scheme-**1**

Synthesis of azomethines:

A series of azomethines **SB**1-**SB**14 were synthesized by the condensation of cyanoethyltertiaryaminobenzaldehydes with aniline or *o*-, *m*-, *p*- fluoro/chloro aromatic amines (Scheme-**2)**.

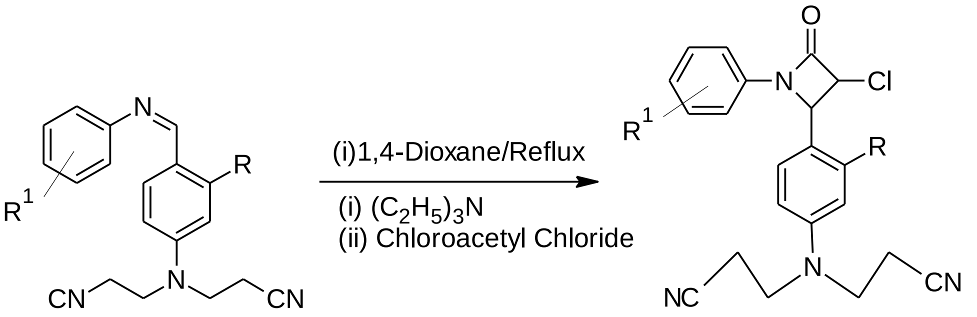


R = -H, -CH$_3$, R^1 = -H or *o*-, *m*-, *p*- (F or Cl) (**SB**1-**SB**14)

Scheme-**2**

Synthesis of 2-azetidinones:

A new series of novel 2-azetidinones **BL**1-**BL**14 was synthesized by incorporation of 2-azetidinone ring at the imine linkage of azomethines (Scheme-**3**).



R = -H, -CH$_3$, R^1 = -H or *o*-, *m*-, *p*- (F or Cl) (**BL**1-**BL**14)

Scheme-**3**

All Results of test compounds are shown in **Tables**

Table 1: Results of the *in-vitro* antimicrobial susceptibility testing observed in azomethines:

S.No.	**Comp. Name**	**Diameter of zone of inhibition in mm**					
		Fungal strains		**Gram "+"ve**		**Gram "-"ve**	
		A. niger	***A. fumigatus***	***B. subtilis***	***S. aureus***	***E. coli***	***P. vulgaris***
1.	SB1	22	18	21	21	23	24
2.	SB2	24	25	24	27	25	27
3.	SB3	19	21	20	22	22	25
4.	SB4	26	27	25	28	26	29
5.	SB5	23	23	23	26	23	26
6.	SB6	18	17	21	23	20	18
7.	SB7	25	26	24	27	24	27
8.	Am	-	-	48	47	49	44
9.	Flu	45	48	-	-	-	-
10.	DMSO	-	-	-	-	-	-

Am = Ampicillin, Flu = Fluconazole, DMSO = Dimethylsulphoxide; Concentration = 600μg/mL

Table 2: Results of the *in-vitro* antimicrobial susceptibility testing observed in azomethines:

S.No.	Comp. Name	Diameter of zone of inhibition in mm					
		Fungal strains		Gram "+"ve		Gram "-"ve	
		A. niger	***A. fumigatus***	***B. subtilis***	***S. aureus***	***E. coli***	***P. vulgaris***
1.	SB8	20	16	21	13	23	23
2.	SB9	22	22	23	24	25	26
3.	SB10	19	21	21	21	22	21
4.	SB11	25	26	24	27	25	28
5.	SB12	20	21	22	22	23	23
6.	SB13	18	17	20	19	20	19
7.	SB14	21	22	20	23	21	24
8.	Am	-	-	48	47	49	44
9.	Flu	45	48	-	-	-	-
10.	DMSO	-	-	-	-	-	-

Am = Ampicillin, Flu = Fluconazole, DMSO = Dimethylsulphoxide, Concentration = 600µg/mL

Table 3: Results of the *in-vitro* antimicrobial susceptibility testing observed in 2-azetidinones:

S.No.	Comp. Name	Diameter of zone of inhibition in mm					
		Fungal strains		Gram "+"ve		Gram "-"ve	
		A.niger	***A. fumigatus***	***B. subtilis***	***S. aureus***	***E. coli***	***P. vulgaris***
1.	BL1	26	25	24	26	23	23
2.	BL2	27	27	26	27	27	25
3.	BL3	24	25	23	26	23	21
4.	BL4	28	28	30	32	29	31
5.	BL5	26	25	27	25	24	27
6.	BL6	24	21	24	23	21	19
7.	BL7	26	25	27	29	27	28
8.	Am	-	-	48	47	49	44
9.	Flu	45	48	-	-	-	-
10	DMSO	-	-	-	-	-	-

Am = Ampicillin, Flu = Fluconazole, DMSO = Dimethylsulphoxide, Concentration = 600µg/mL

Table 4: Results of the *in-vitro* antimicrobial susceptibility testing observed in 2-azetidinones:

S.No.	Comp. Name	Diameter of zone of inhibition in mm					
		Fungal strains		Gram "+"ve		Gram "-"ve	
		A. niger	***A. fumigatus***	***B. subtilis***	***S. aureus***	***E. coli***	***P. vulgaris***
1.	BL8	24	18	23	22	23	24
2.	BL9	25	24	26	27	26	27
3.	BL10	23	20	24	24	24	25
4.	BL11	26	26	25	25	25	24
5.	BL12	24	24	25	26	23	27
6.	BL13	22	19	23	23	21	20
7.	BL14	25	25	23	20	23	21
8.	Am	-	-	48	47	49	44
9.	Flu	45	48	-	-	-	-
10.	DMSO	-	-	-	-	-	-

Am = Ampicillin, Flu = Fluconazole, DMSO = Dimethylsulphoxide, Concentration = 600µg/mL

Table 5: Physical data of cyanoethyltertiaryaminobenzaldehydes A and B:

S.No.	Comp.	R	Yield (%)	m.p.(^{o}C)	Molecular Formula
1.	**A**	-H	62.01	104	$C_{13}H_{13}N_3O$
2.	**B**	$-CH_3$	61.12	97	$C_{14}H_{15}N_3O$

Table 6: Physical data of azomethines SB1-SB14:

S.No.	Comp.	R^{1}	R	m.p.^{0}C	Yield (%)	Molecular Formula
1.	SB1	Aniline	H	170	62.84	$C_{19}H_{18}N_4$
2.	SB2	2-Fluoroaniline	H	91	58.14	$C_{19}H_{17}FN_4$
3.	SB3	3-Fluoroaniline	H	98	58.76	$C_{19}H_{17}FN_4$
4.	SB4	4-Fluoroaniline	H	106	59.89	$C_{19}H_{17}FN_4$
5.	SB5	2-Chloroaniline	H	101	62.46	$C_{19}H_{17}ClN_4$
6.	SB6	3-Chloroaniline	H	106	60.83	$C_{19}H_{17}ClN_4$
7.	SB7	4-Chloroaniline	H	106	63.56	$C_{19}H_{17}ClN_4$
8.	SB8	Aniline	CH_3	122	63.52	$C_{20}H_{20}N_4$
9.	SB9	2-Fluoroaniline	CH_3	137	60.04	$C_{20}H_{19}FN_4$
10.	SB10	3-Fluoroaniline	CH_3	136	59.62	$C_{20}H_{19}FN_4$
11.	SB11	4-Fluoroaniline	CH_3	140	57.89	$C_{20}H_{19}FN_4$
12.	SB12	2-Chloroaniline	CH_3	139	61.85	$C_{20}H_{19}ClN_4$
13.	SB13	3-Chloroaniline	CH_3	126	60.65	$C_{20}H_{19}ClN_4$
14	SB14	4-Chloroaniline	CH_3	98	52.09	$C_{20}H_{19}ClN_4$

Table 7 Physical data of 2-azetidinones BL1-BL14:

S.No.	Comp.	R^{1}	R	m.p.^{0}C	Yield %	Molecular Formula
1.	BL1	Aniline	H	85	60.23	$C_{21}H_{19}ClN_4O$
2.	BL2	2-Fluoroaniline	H	100	64.14	$C_{21}H_{18}ClFN_4O$
3.	BL3	3- Fluoroaniline	H	105	62.62	$C_{21}H_{18}ClFN_4O$
4.	BL4	4-Fluoroaniline	H	102	58.23	$C_{21}H_{18}ClFN_4O$
5.	BL5	2-Chloroaniline	H	84	65.42	$C_{21}H_{18}Cl_2N_4O$
6.	BL6	3-Chloroaniline	H	98	62.81	$C_{21}H_{18}Cl_2N_4O$
7.	BL7	4-Chloroaniline	H	66	60.16	$C_{21}H_{18}Cl_2N_4O$
8	BL8	Aniline	CH_3	120	53.31	$C_{22}H_{21}ClN_4O$
9.	BL9	2-Fluoroaniline	CH_3	110	52.44	$C_{22}H_{20}ClFN_4O$
10.	BL10	3-Fluoroaniline	CH_3	106	44.61	$C_{22}H_{20}ClFN_4O$
11.	BL11	4-Fluoroaniline	CH_3	92	48.63	$C_{22}H_{20}ClFN_4O$
12.	BL12	2-Chloroaniline	CH_3	140	47.26	$C_{22}H_{20}Cl_2N_4O$
13.	BL13	3-Chloroaniline	CH_3	130	49.53	$C_{22}H_{20}Cl_2N_4O$
14.	BL14	4-Chloroaniline	CH_3	102	54.46	$C_{22}H_{20}Cl_2N_4O$

It is clearly evident from table 1 and 2 that in azomethines series compound **SB**4 bearing *p*-fluoro group exhibited activity against pathogens in order *P. vulgaris* > *S. Aureus* > *A. fumigates* > *A. niger* > *E. coli* > *B. subtilis* with zone of inhibition from 29 mm to 25 mm. Compounds **SB**7 bearing *p*-chloro group also exhibited good activity against the *P. vulgaris* with zone of inhibition of 27 mm to 24 mm.

Table 5.3 and 5.4 shows the antimicrobial screening results of 2-azetidinones which indicate that compound **BL**4 and **BL**7 bearing *p*-fluoro group exhibited better activity against *S. aureus* with zone of inhibition of 32 mm.

All the tested azomethines showed the best results against *P. vulgaris* and *A. fumigates*. The increased values shown by **BL**4 and **BL**7 are due to the incorporation of 2-azetidinone nucleus on imine linkage of azomethines, which leads to a enhancement in the zone of inhibition as compared to the azomethines. Compounds having *m*-fluoro and *m*-chloro substitution exhibited poor activities as compared to standard drugs. The substitution of methyl group on the azomethines and 2-azetidinones leads to the decrement of biological activity.

CONCLUSION

Present studies demonstrate the synthesis and antimicrobial susceptibility testing of a series of azomethines and novel 2-azetidinones derived from cyanoehthyltertiary-aminobenzaldehydes. These compounds exhibited promising antimicrobial activity. The antimicrobial activity studies showed significant activity as compared to standard. It can be concluded that this class of compounds holds great promise towards good active leads in medicinal chemistry. These efforts creates opening of a new interest in, this class of compounds in the field of antimicrobials. Thus in future, this class of compounds may be used as templates for generating better lead molecules.

ACKNOWLEDGEMENT

Authors gratefully acknowledge to Defence Research Development Establishment Gwalior and ITM University Gwalior for spectral characterisations. Authors also wish to acknowledge the help rendered by Prof. Rajeev Jain, SOS in Chemistry, Jiwaji University Gwalior, for bringing this manuscript in the present form.

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