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Synthesis, Characterisation and Antimicrobial Screening of Some Cyanoethylated Bioactive Azomethines and β-Lactams

Pradeep K Soni* and Anand K Halve

Department of Chemistry, Jiwaji University, India

***Corresponding author:** Pradeep K. Soni, School of Studies in Chemistry, Jiwaji University, Gwalior, India– 474011

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Abstract

A library of azomethines SB1-SB10 has been synthesized by the condensation of 3,3'-((4-formyl-3-methoxyphenyl)azanediyl)dipropanenitrile (C) with aniline, fluoro-, chloro- and bromo- anilines. Azomethines at the imine linkage on reaction with chloroacetylchloride and triethylamines in 1,4-dioxan afforded a series of novel β-lactams BL1-BL10. 3,3'-((4-formyl-3-methoxyphenyl)azanediyl) dipropanenitrile (C) was synthesized by cyanoethylation of the m-anisidine followed by formylation in presence of $POCl_3$ and DMF. All compounds were characterized by elemental analysis, FT-IR and ^{1}HNMR data and screened *in-vitro* for their activity against *S. aureus, B. subtilis, P. vulgaris, E. coli, A. niger* and *A. fumigatus*. Most of the compounds showed significant activity against microorganisms tested.

Keywords: β-lactams; Azomethines; Tertiary-amino-benzaldehyde; Cyanoethylation; Antimicrobial activity

Abbreviations: RAND: Research and Development; Anti-MHV: Anti-Mouse Hepatitis Virus; HSV-1: Herpes Simplex Virus Type-1; AD-5: Adenovirus Type-5; DMSO: Dimethyl Sulfoxide; MIC: Minimum Inhibitory Concentration; DMF: Dimethyl Formamide; TMS: Tetramethyl Silane

Introduction

Pathogenic micro-organisms have been engaged in an evolutionary battle with the humans and animals since the dawn of time. Every time a new developed antimicrobial resistance is followed. This is posing a serious challenge to scientific community and greatest threat to human health. Antibiotic resistance has increased dramatically in the last few decades. Most of the antibiotics currently in use were discovered in the 'Golden era' of antibiotics. World Health Organization [1] has declared that "The world is moving towards a post-antibiotic era in which common infections will once again kill". By estimation of the RAND (Research and Development) Corporation 10 million people world-wide could die from resistant micro-organisms in 2050 which is more than from cancer. There is always need for the safer antibacterial agents and research efforts are going on for developing better and more effective antibacterial agents. Antimicrobial agents containing β-lactams has become an integral part of the chemotherapeutic arsenal available to today's medical practitioners. Azomethines and their derivatives has been a research subject [2] due to their pharmacological applications [3,4] and striking complex-metric behaviour. These properties allow them to play a pivotal role in various biological activities [5,6] viz. Anti-bacterial [7] antiviral [8], antifungal [9], anthelmintic [10], anti-amoebic [11], anti-inflammatory [12], analgesic [13], anti-mouse hepatitis virus (MHV) [14], inhibition of herpes simplex virus type-1 (HSV-1), adenovirus type-5 (AD-5) [15] anti-malarial [16] and herbicidal [17] activities. β-Lactams are well-known heterocyclic compounds among the organic and medicinal chemists. Biological activities of the famous antibiotics such as penicillin's, cephalosporins and carbapenems are attributed to the presence of β-lactam ring in them. Some other types of biological activity besides the antibacterial activity have been reported in compounds containing β-lactams ring [18]. Such biological activities include antimicrobial [19], anti-tubercular [20], carbonic anhydrase inhibitors [21], anti-convulsant [22], anti-inflammatory [23], anthelmintic [24] and hypoglycaemic activities [25]. The β-lactams also serve as synthase for biologically important classes of organic compounds [26]. We have also prepared some azomethines and β-lactams containing cyanoethyl groups previously displaying good antimicrobial activities [27]. Azomethines formed by 3,3'-((4-formyl phenyl) azanediyl)dipropanenitrile and their stable complexes with some metals have been reported by Arora et al. [28]. A new series of complexes of dioxo-uranium (IV) with the azomethines (E)-3,3'-((4-((phenylimino)methyl)phenyl)azanediyl)dipropanenitrile derived from N-[(4-N'N-bis-(2'cyanoethyl aminobenzylideneamino] benzaldehyde and aniline were prepared by Arora et al. [29] It is well known that the introduction of fluorine atom into an organic

molecule causes dramatic changes in its biological activity profile, mainly due to high electro negativity of fluorine, the strong carbon-fluorine bond and increased solubility in lipids. Azomethines containing chloro and cyano groups display enhanced antibacterial activities [30]. It was thought worthwhile to incorporate cyanoethyl moiety and halogen groups to the β-lactam nucleus and study in-vitro their biological potential.

Materials and Methods

Melting points were determined in an open capillary tube and are uncorrected. The chemicals and solvents used were of laboratory grade and were 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. 1HNMR spectra were recorded in DMSO-d6 with an advanced spectrophotometer (Bruker) at 400-MHz frequency using TMS as an internal standard. Elemental analyses were performed on a Perkin-Elmer-240, elemental analyzer. All the synthesized compounds were purified by re-crystallization in ethanol.

Preparation of 3,3'-((4-formyl-3-methoxyphenyl) azanediyl)dipropanenitrile

Cyanoethylation of m-anisidine; Formation of 3,3'-((3-methoxyphenyl) azanediyl) dipropanenitrile: A mixture of freshly distilled m-anisidine (0.1mol), acrylonitrile (0.4mol) glacial acetic acid (0.33mol) and freshly prepared cuprous chloride (1.5g) were gently refluxed for twelve hours. The liquid mixture was cooled and poured with stirring into liquor ammonia (100ml) and mixture was left aside overnight. The solid formed was washed well with water till free from copper salts. The solid was filtered and re-crystallized from ethanol when 3,3'-((3-methoxyphenyl)azanediyl)dipropanenitrile was obtained as colourless needles.

Formylation of 3,3'-((3-methoxyphenyl)azanediyl) dipropanenitrile; Formation of 3,3'-((4-formyl-3-methoxyphenyl)azanediyl)dipropanenitrile(C): N'N-bis-2'-cyanoethyl-m-anisidine (0.04 mol) was slowly added to a cooled mixture of phosphorous oxy-chloride (0.04 mol) and dimethyl formamide (0.16 mol) taken in a round bottomed flask provided with a mechanical stirrer and a reflux condenser carrying a calcium chloride guard tube. The contents were heated on a steam bath for three hours while the mixture was stirred. The dark mixture was cooled and poured over crushed ice and the solution neutralised with crystalline sodium acetate the content were set aside overnight; when the solid product separated out. It was filtered under suction, washed well with water and recrystallized from ethanol when the aldehyde (C) was obtained as light yellow needles. Elemental analysis data of 3,3'-((4-formyl-3-methoxyphenyl) azanediyl)dipropanenitrile (C): Molecular Formula; $C_{14}H_{15}N_3O_2$, Yield 64.14%, Elements; Required (Found %): C 65.35(64.90), H 5.88(5.73), N 16.33(16.02). Spectral data; Groups (FT-IR absorption frequencies cm^{-1} in KBr): CHO (1676.5), N-CH_2 (2249.1), CH_2CN (2744.2) OCH_3(1716.5), CH (Ar)(2971.8). 1H NMR-Spectra in DMSO-d6: Protons signal groups (δ ppm): 3HS OCH_3(3.828), 4HT CH_2CN(2.795-2.829), 4HT CH_2CH_2CN(3.814-3.848), 1HD Ar(6.996-7.018), 1HS Ar(7.216), 1HD Ar(7.717-7.739), 1HS CHO (9.734).

General procedure for the preparation of azomethines SB1-SB10

Solution of an aldehyde (C) (0.0103 mol) and appropriate amine (0.0103 mol) in ethanol with 1-2 drops of concentrated H_2SO_4, were refluxed over eight hours, mixture was cooled overnight and transferred into crushed ice with addition of 1-2 drops of concentrated sulphuric acid. After one hour precipitate was obtained by filtration and washing two times with distilled water, dried into air and re-crystallized with ethanol, azomethines obtained as yellow crystals. Elemental analysis of (Z)-3,3'-((4-(((2-fluorophenyl)imino)methyl)-3-methoxy-phenyl)-azanediyl) dipropanenitrile (Azomethine-SB2): Molecular Formula; $C_{20}H_{19}FN_4O$, Yield 54.18% Elements; Required (Found %); C 68.56(68.26), H 5.47(5.36), N 15.99(15.42). Spectral data; Groups (FT-IR absorption frequencies cm^{-1} in KBr): C=N (1679.6), N-CH_2-(2249.1), CH_2-CN(2744.2), OCH_3(1760.5), CH Ar (2973.6). ^{1}H NMR-Spectra in DMSO-d6: Proton signal groups (δ ppm) 3HS OCH3 (3.801), 4HT CH_2CN(2.781-2.816), 4HT CH_2CH_2CN(3.795-3.829), 1HS Ar(6.752), 1HD Ar(6.758-6.822), 2HD Ar(7.628-7.650), 3HD (3) Ar(8.754-8.853), 1H CH=N(9.935).

General procedure for the preparation of β-lactams BL1-BL10

Table 1: Physical data of azomethines (SB1-SB10).

S.No.	Comp. Name	R	m.p.^{0}C	Yield (%)	Molecular formula
1.	SB1	Aniline	155	64.45	$C_{20}H_{20}N_4O$
2.	SB2	2-Fluoroaniline	142	54.18	$C_{20}H_{19}FN_4O$
3.	SB3	3-Fluoroaniline	137	56.42	$C_{20}H_{19}FN_4O$
4.	SB4	4-Fluoroaniline	182	54.86	$C_{20}H_{19}FN_4O$
5.	SB5	2-Chloroaniline	134	64.91	$C_{20}H_{19}ClN_4O$
6.	SB6	3-Chloroaniline	136	65.53	$C_{20}H_{19}ClN_4O$
7.	SB7	4-Chloroaniline	125	45.74	$C_{20}H_{19}ClN_4O$
8.	SB8	2-Bromoaniline	156	66.56	$C_{20}H_{19}BrN_4O$
9.	SB9	3-Bromoaniline	143	67.23	$C_{20}H_{19}BrN_4O$
10.	SB10	4-Bromoaniline	180	65.41	$C_{20}H_{19}BrN_4O$

A mixture of azomethines (0.0047mol) and tri-ethylamine (0.0047mol) was dissolved in 1,4-dioxane (50mL) with stirring and cooled. Chloroacetylchloride (0.0047mol) was added drop wise within a period of 30 minutes. The reaction mixture was stirred further for 8-12 hours at 50-70^{0}C. 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 re-crystallized using ethanol. β-lactams were obtained as dark coloured crystals. Elemental analysis data of 3-[{4-[3-chloro-1-(2-fluorophenyl)-4-oxoazetidin-2-yl]-3-methoxyphenyl}(2-isocyanoethyl)amino]propanenitrile (β-lactam BL2): Molecular Formula; $C_{22}H_{20}ClFN_4O_2$, Yield 63.31%, Elements; Required (Found %); C 61.90(60.36), H 4.72(4.26), N 13.12 (12.01). Spectral data; Groups (FT-IR absorption frequencies in cm^{-1} KBr): C=O(1749.2), OCH_3 (1605.2), CH_2-C-CN(2249.1), CH_2CN(2039.9), CH-Ar(2981.7). ^1H NMR spectra in DMSO-d6: Protons signals (Groups) (δ ppm) 4HT CH_2CN(2.810-2.844), 4HT CH_2CH_2CN(3.829-3.864), 3HS OCH_3(3.929), 1HD CH of β-lactam Ring (5.232-5.253), 1HD CHCl of β-lactam Ring (5.631-5.659), 1HS Ar(6.379), 1HD Ar(6.479-6.483), 1HD Ar(7.531-7.553), 1HD Ar(8.689), 1HD Ar(8.747), 1HT Ar(8.884), 1HT Ar(8.921) (Table 1,2).

Table 2: Physical data of β-lactams (BL1-BL10).

S.No	Comp. Name	R	m.p.°C	Yield %	Molecular Formula
1.	BL1	Aniline	140	66.23	$C_{22}H_{21}ClN_4O_2$
2.	BL2	2-Fluoroaniline	145	63.31	$C_{22}H_{20}ClFN_4O_2$
3.	BL3	3-Fluoroaniline	132	59.25	$C_{22}H_{20}ClFN_4O_2$
4.	BL4	4-Fluoroaniline	165	62.62	$C_{22}H_{20}ClFN_4O_2$
5.	BL5	2-Chloroaniline	162	65.13	$C_{22}H_{20}Cl_2N_4O_2$
6.	BL6	3-Chloroaniline	135	64.53	$C_{22}H_{20}Cl_2N_4O_2$
7.	BL7	4-Chloroaniline	141	60.52	$C_{22}H_{20}Cl_2N_4O_2$
8.	BL8	2-Bromoaniline	93	64.61	$C_{22}H_{20}BrClN_4O_2$
9.	BL9	3-Bromoaniline	82	62.28	$C_{22}H_{20}BrClN_4O_2$
10.	BL10	4-Bromoaniline	130	61.44	$C_{22}H_{20}BrClN_4O_2$

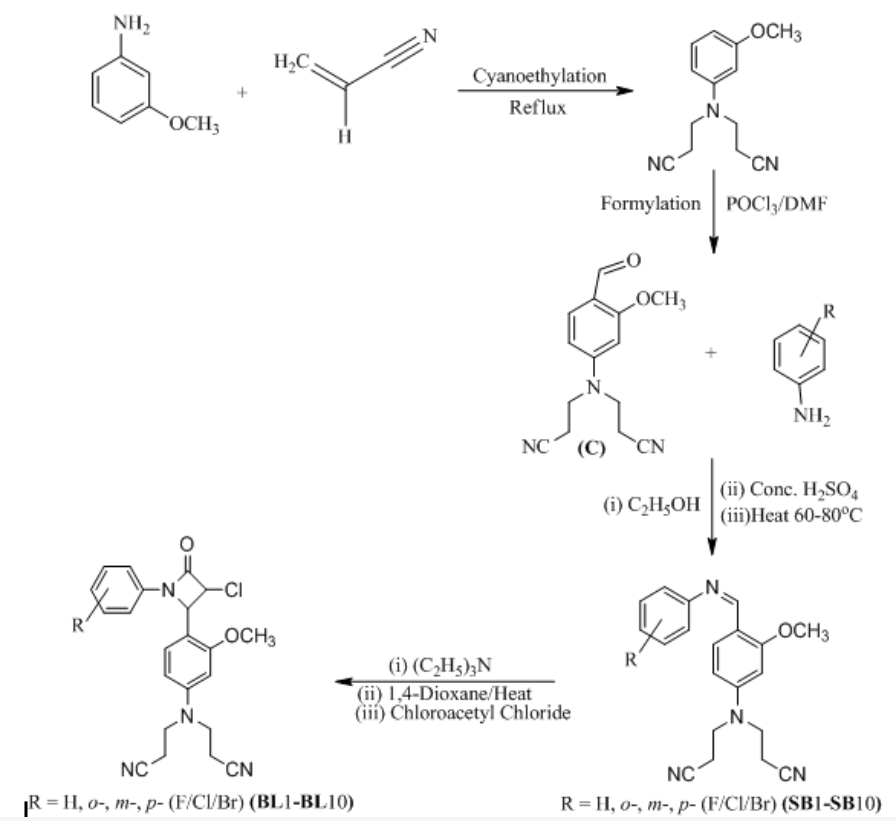

Figure 1: Route for the synthesis of azomethines and β-lactams.

Antimicrobial susceptibility testing

All the synthesized azomethines SB1-SB10 and β-lactams BL1-BL10 were subjected to *in-vitro* antimicrobial susceptibility testing against *Stayphylococcus aureus, Bacillus subtilis* (Gram "+"ve) *Proteus vulgaris, Escherichia coli* (Gram "-"ve); bacterial and *Aspergillus niger, Aspergillus fumigatus* fungal strains in order to determine their efficacy and structure-activity relationship taking ampicillin as broad-spectrum antibacterial and fluconazole as an anti-fungal 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 2-5mL nutrient Mueller-Hinton agar medium (for bacterial strains) and Sabourauds broth (for fungal strains) were grown for 2.5h. After the inoculums dried, 6mm diameter wells were made in the agar plate with a sterile cork borer. The compounds were dissolved in DMF at concentration of 300µg/mL. The Petri plates were incubated at 37 ˚C for 24hours. The Zone of inhibition was measured in mm to estimate the potency of the test compounds.

Results and discussion

All the compounds SB1-SB10 and BL1-BL10 were synthesized according to Figure 1 and subjected to *in-vitro* antimicrobial susceptibility testing against *Stayphylococcus aureus, Bacillus subtilis, Proteus vulgaris, Escherichia coli, Aspergillus niger* and *Aspergillus fumigatus* strains in order to determine structure-activity relationship taking ampicillin and fluconazole as broad-spectrum antibacterial and antifungal standard drugs respectively. The zone of inhibition around the disc against the tested pathogens was determined at 300 µg/mL concentration by disc diffusion assay.

Table 3: 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	15	13	12	13	13	16
2.	SB2	19	18	19	21	20	22
3.	SB3	17	17	16	16	15	20
4.	SB4	17	20	18	24	23	23
5.	SB5	16	18	16	19	17	22
6.	SB6	12	13	13	11	14	12
7.	SB7	19	22	19	20	18	23
8.	SB8	12	16	18	20	19	22
9.	SB9	10	17	16	19	20	21
10.	SB10	11	13	13	14	17	16
11.	Amp	-	-	34	33	33	35
12.	Fluc	35	36	-	-	-	-
13.	DMSO	-	-	-	-	-	-

Amp = Ampicillin, Fluc = Fluconazole, DMSO = Dimethyl sulfoxide; Concentration = 300µg/mL

It is clearly evident from Table 3 that azomethine SB4 bearing p-fluoro group exhibited good activity against the microorganisms used in the present study in order *S. Aureus* > *E. coli* = *P. vulgaris* > *A. fumigatus* > *B. subtilis* > *A. niger*. Moreover this compound shows clear zone of inhibition of 24mm (against *S. Aureus*), 23mm (against *E. coli* and *P. vulgaris*), 20mm (against *A. fumigatus*), 18mm (against *B. subtilis*) and 17mm (against *A. niger*).

Compound SB7 (Table 3) bearing p-chloro group exhibited moderate activity against tested microorganisms in order *P. vulgaris* > *A. fumigatus* > *S. aureus* > *A. niger* = *B. subtilis* > *E. coli* slight lesser than p-fluoro substituted compounds. This compound showed clear zone of inhibition of 23mm (against *P. vulgaris*), 22mm (against *A. fumigatus*), 20mm (*S. aureus*) 19mm (against *A. niger* and *B. subtilis*) 18mm (against *E. coli*).

Table 4 shows the antimicrobial screening results of β-lactam derivatives which clearly indicate that compound BL4 (Table 4) bearing p-fluoro group exhibited better activity against the tested microorganisms in order *S. aureus* > *P. vulgaris* > *E. coli* > *B. subtilis* > *A. niger* > *A. fumigatus* with clear zone of inhibition of 27mm (against *S. aureus*), 26mm (against *P. vulgaris*), 25mm (against *E. coli*), 23mm (against *B. subtilis*), 22mm (against *A. niger*) and 20mm (against *A. fumigatus*).

Table 4: Results of the *in-vitro* antimicrobial susceptibility testing observed in β-lactams (BL1-BL10).

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	18	15	17	20	13	19
2.	BL2	19	17	22	21	20	23
3.	BL3	20	19	16	20	16	19
4.	BL4	22	20	23	27	25	26
5.	BL5	17	18	18	20	20	23
6.	BL6	14	17	14	19	15	16
7.	BL7	21	19	22	19	25	20
8.	BL8	18	17	20	20	18	21
9.	BL9	16	18	15	17	14	18
10.	BL10	20	18	20	17	23	19
11.	Amp	-	-	41	38	37	42
12.	Fluc	39	36	-	-	-	-
13.	DMSO	-	-	-	-	-	-

Amp = Ampicillin, Fluc = Fluconazole, DMSO = Dimethylsulphoxide; Concentration = 300µg/mL

It is also indicated by Table 4 that compound BL7 bearing p-fluoro group exhibited good activity against the tested microorganisms in order *E. coli* > *B. subtilis* > *A. niger* > *P. vulgaris* > *A. fumigatus* > *S. aureus* with clear zone of inhibition of 25mm (against *E. coli*), 22mm (against *B. subtilis*), 21mm (against *A. niger*) 20mm (against *P. vulgaris*) 19mm (against *S. aureus* and *A. fumigatus*) (Figure 1).

Conclusion

The study demonstrates that a series of azomethines and novel β-lactams were synthesized from 3,3'-((4-formyl-3-methoxyphenyl)azanediyl)dipropanenitrile by the condensation with corresponding aromatic amine. Novel β-lactams were derived by electro cyclization at the imine linkage of azomethines and were evaluated as bioactive agents. The newly synthesized compounds exhibited promising antimicrobial activity using disc diffusion method. The studies showed significant activity as compared to standard. It can be concluded that this class of compounds holds 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.

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