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Synthesis, Characterisation of some 2-azetidinone derivatives from 2,6-diaminopyridine and evaluation of their antimicrobial activity

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Abstract: A series of Schiff base and 2-azetidinones of 2,6diaminodipyridine have been synthesized. 2,6diaminodipyridine was condensed with various aromatic aldehyde in ethanol. These Schiff's bases on treatment with chloroacetylchloride in the presence of triethylamine gave substituted 2-azetidinone **(3a-3g)**.The chemical structures of the synthesized compounds were confirmed by means of IR, 1H-NMR, elemental analysis and Mass. The synthesized compounds showed good antibacterial activity such as Staphylococcus aureus , Bacillus subtilis, Escherichia coli and Klebsiella pneumonia.
Key Words: 2,6-diaminodipyridine, Schiff base, Azetidinone, Antibacterial.

Introduction

The synthesis of heterocyclic compound has always drawn the attention of chemist over the years mainly because of their important biological properties [1]. Particularly, 2-Azetidinone or β-lactums are well known class of heterocyclic compounds among organic and medicinal chemistry [2]. The most widely used antibiotics such as the penicillin, cephalosporin, carumonam, aztreonam, thienamycine and the nocardicins all contain β-lactam rings [3]. Besides their antibiotic activity azetidinones are also known to exhibit some other types of biological activities[4], such as antibacterial[5] ,antimicrobial[6], antitubercular [7], local anesthetic[8], anti-nflammatory[9], anti-convulsant[10], anti-viral[11], anticancer[12].They also function as enzyme inhibitors and are effective on central nervous system[13]. Pyridine derivatives were reported to possess antimicrobial [14] activities. Therefore it was envisaged that compounds containing both the chemical moieties would result in compounds of interesting biological activities.

In this present study 2,6-diaminopyridine was treated with different substituted aromatic aldehydes to produce Schiff bases. The Schiff bases were subjected to addition reactions with chloroacetyl chloride in presence of triethyl amine in DMF to produce 2-azetidinone derivatives respectively. The chemical structures of the synthesized compounds were confirmed by means of IR, ^{1}H-NMR , elemental analysis and Mass. The synthesized compounds were screened for antibacterial(Staphylococcus aureus, Escherichia coli)

Experimental

The IR spectra of the ligand were recorded with a Jasco-FT/IR-4200 instrument in KBr pellets.^{1}H NMR spectra of compounds in DMSO-d6 solution were recorded on a Bruker 400MHz spectrometer and chemical shifts are indicated in ppm relative to tetramethylsilane.Mass spectra were recorded using a KRATOS MS50TC spectrometer. Melting points were measured by Melting point apparatus (Stuart SMP30). Elemental analysis was performed on Elementar vario Micro Cube.

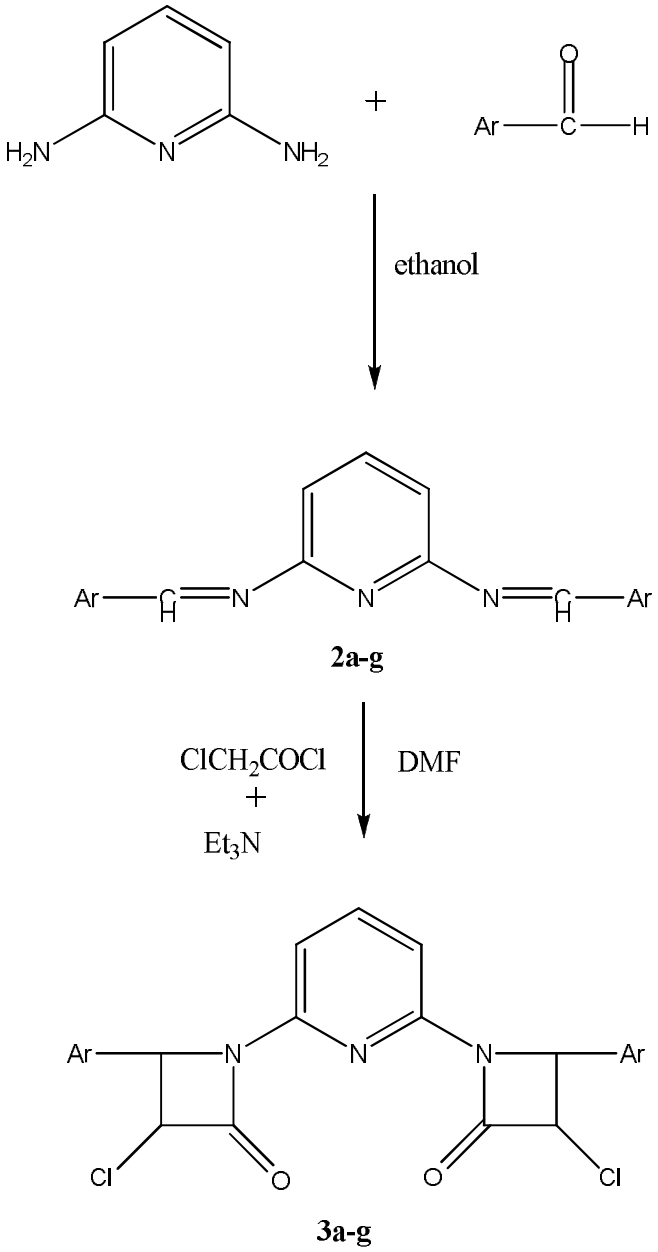
General Methods of Synthesis

1.Synthesis of Schiff Bases:(2a-2g)

2,6-diaminopyridine (0.1 mol), various substituted aromatic aldehydes (0.2 mol) were refluxed in ethanol (50 mL)for about 5 h. The solid mass thus obtained was recrystallized from ethanol.

2.Synthesis of substituted azetidinones:(3a-3g)

A mixture of Schiff base (0.01 mol) and triethyl amine (0.02mol) were dissolved in DMF (50 ml)at 0-5 C. To this mixture ,chloroacetyl chloride (0.02mol) was added drop wise for 30 min, then stirred for further 3 h and left at room temperature for 48 h, the precipitated amine hydrochloride was filtered off .The filtrate then poured into ice cold water, filtered off, dried and recrystalised from DMF:ethanol(2:8).



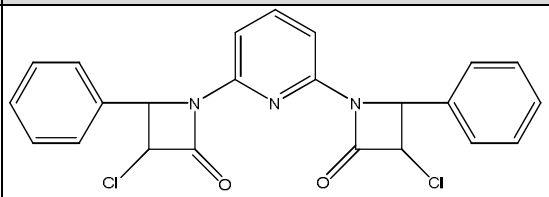
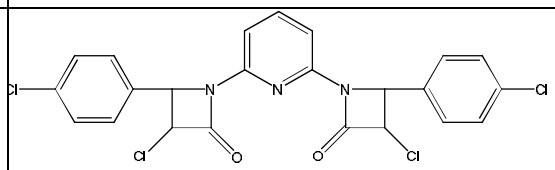
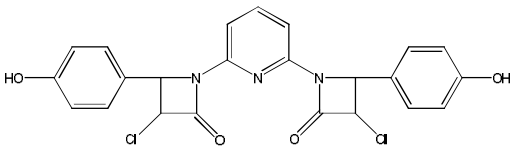
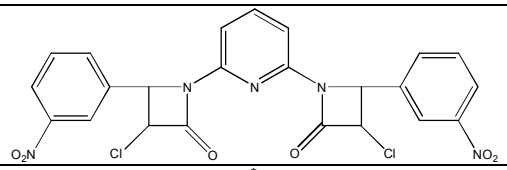
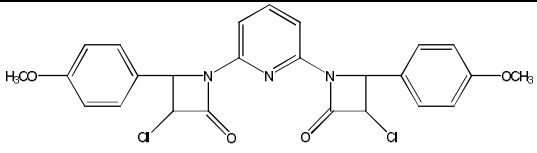
Ar= (a)phenyl;(b) 4-chlorophenyl;(c) 4-hydroxyphenyl;(d) 3-nitrophenyl; (e)4-methoxyphenyl;(f) 4-dimethylamino phenyl;(g) 4-methylphenyl

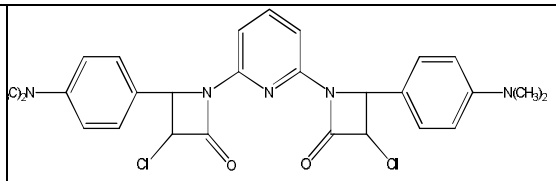
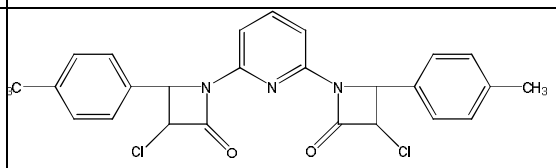
Scheme 1. :Synthesis of compounds:(3a-3g)

Table (I) : Physical properties and Elemental Analysis (C.H.N) of synthesis Compounds :(3a-3g)

Comp. No.	*Molecular formula*	Molecular Weight	M.P (^{0}C)	Yield (%)	Elemental analysis Cal(found)		
					C%	H%	N%
3a	$C_{23}H_{17}Cl_2N_3O_2$	438	289 ^{0}C	65%	63.03 (63.67)	3.91 (3.50)	9.59 (9.62)
3b	$C_{23}H_{15}Cl_4N_3O_2$	507	300 ^{0}C<	60%	54.47 (54.02)	2.98 (2.44)	8.28 (8.41)
3c	$C_{23}H_{17}Cl_2N_3O_4$	470	287 ^{0}C	59%	58.74 (59.24)	3.64 (3.13)	8.93 (8.48)
3d	$C_{23}H_{15}Cl_2N_5O_6$	528	287^{0}C	63%	52.29 (52.98)	2.86 (2.33)	13.26 (13.94)
3e	$C_{25}H_{21}Cl_2N_3O_4$	498	291^{0}C	61%	60.25 (59.50)	4.25 (3.98)	8.43 (7.97)
3f	$C_{27}H_{27}Cl_2N_5O_2$	524	300 ^{0}C<	64%	61.84 (62.25)	5.19 (5.66)	13.35 (13.82)
3g	$C_{25}H_{21}Cl_2N_3O_2$	466	295^{0}C	66%	64.39 (65.02)	4.54 (5.05)	9.01 (9.49)

Table (II) $_1$H-NMR and FT-IR Spectral data for compounds (3a-3g)

Comp. No.	Compd. Structure	1H-NMR spectra data (DMSO-d6) ppm	IR- spectra data (KBr) cm^{-1}
3a		7.89-8.19(m,3H;CH Pyridine), 7.11-7.56(m,10H;CH benzene), 5.66(d,2H ,2N-CH-C), 4.52 (d,2H,2C-CH-Cl).	3021(Ar-CH), 1700(C=O), 1623(C=N),1580(C=C), 808(CH-Cl)
3b		7.86-8.12(m,3H;CH Pyridine), 7.16-7.11(m,8H;CH benzene), 5.23(d,2H ,2N-CH-C), 4.41 (d,2H,2C-CH-Cl).	3010(Ar-CH), 1710(C=O), 1613(C=N),1575(C=C), 788(CH-Cl)
3c		7.79-8.05(m,3H;CH Pyridine), 7.07-7.54(m,8H;CH benzene), 5.28(d,2H ,2N-CH-C), 4.35(d,2H,2C-CH-Cl), 9.88(s,2H,2OH).	3200(OH),3040(Ar-CH), 1720(C=O), 1610(C=N),1550(C=C), 820(CH-Cl)
3d		7.87-8.06(m,3H;CH Pyridine), 7.02-7.46(m,8H;CH benzene), 5.26 (d,2H ,2N-CH-C), 4.37 (d,2H,2C-CH-Cl).	3015(Ar-CH), 1695(C=O), 1630(C=N),1565(C=C), 810(CH-Cl)
3e		7.91-8.04(m,3H;CH Pyridine), 7.27-7.78(m,8H;CH benzene), 5.28(d,2H ,2N-CH-C), 4.52 (d,2H,2C-CH-Cl), 3.85(s,6H,2OCH$_3$).	3025(Ar-CH), 2870(C-H aliphatic),1705(C=O), 1623(C=N),1570(C=C), 808(CH-Cl)

3f		7.90-8.03(m,3H;CH Pyridine), 7.04-7.49(m,8H;CH benzene), 5.25(d,2H ,2N-CH-C), 4.43(d,2H,2C-CH-Cl), 3.4(s,12H,2($N(CH_3)_2$).	3030(Ar-CH), 2860(C-H aliphatic), 1710(C=O), 1615(C=N),1585(C=C), 820(CH-Cl)
3g		7.88-8.02(m,3H;CH Pyridine), 7.03-7.58(m,8H;CH benzene), 5.29(d,2H ,2N-CH-C), 4.44 (d,2H,2C-CH-Cl), 1.59(s,6H,2CH_3).	3030(Ar-CH), 1720(C=O), 2880(C-H aliphatic), 1620(C=N),1570(C=C), 808(CH-Cl)

Result and Discussion

All the synthesized compounds were first purified by successive recrystallization using appropriate solvents Then the synthesised compounds were subjected to spectral analysis such as FT/IR ,1H- NMR, and elemental analysis to confirm the structures .All the analytical structures show satisfactory result . The following peaks confirmed the formation of 2-azetidinones . The peaks at 1720-1695cm^{-1}, 810-800cm^{-1}, in FTIR have shown the groups of C=O, CH-Cl, in 2-azetidinones respectively . In H-NMRSpectra the peaks at 4.35-4.52ppm and 5.23-5.66ppm for C-CH-Cl,N-CH-C groups have confirmed the formation of 2-azetidinones.

Antimicrobial activity:

The antimicrobial activity of both categories of compounds was determined by the disc diffusion method. The in vitro antimicrobial activity was carried out in two gram positive bacteria, and two gram negative bacteria.The gram positive bacteria used were Staphylococcus aureus and Bacillus subtilis, gram negative bacteria used were Escherichia coli and Klebsiella pneumonia.

The compounds were tested at a concentration of 250,500,1000 ppm in Dimethylsulfoxide. The zone of inhibition was compared after 24 h of incubation at 37° against Streptomycin 1000 ppm as standards for comparison of antibacterial activity (Table III). In general, all synthesized compounds exhibited good inhibitory activity against tested pathogenic microorganism (**S. aureus, B. subtilis, E. coli, K. pneumonia)** peculiar against (**S. aureus, B.subtilis**).

Table (III): Antimicrobial activity for prepared compounds

compounds	**3a**			**3b**			**3c**			**3d**		
	250 ppm	500 ppm	1000 ppm	250 ppm	500 ppm	1000 ppm	250 ppm	500 ppm	1000 ppm	250 ppm	500 ppm	1000 ppm
B. subtilis	+	++	+++	+	++	+++	++	++	+++	+	++	++++
S. aureus	++	+++	++++	++	++	++++	++	+++	++++	++	+++	++++
K. pneumonia	−	+	++	+	++	+++	+	++	+++	−	+	+++
E.Coli	-	+	++	+	++	+++	−	++	+++	+	++	+++
compounds	**3e**			**3f**			**3g**			**Streptomycin**		
	250 ppm	500 ppm	1000 ppm	250 ppm	500 ppm	1000 ppm	250 ppm	500 ppm	1000 ppm	250 ppm	500 ppm	1000 ppm
B. subtilis	++	++	+++	++	++	+++	++	++	+++	++	+++	++++
S. aureus	++	+++	++++	++	+++	++++	++	+++	++++	++	+++	++++
K. pneumonia	−	+	++	+	++	+++	−	++	+++	++	+++	++++
E.Coli	−	++	+++	+	++	+++	+	++	+++	++	+++	++++

Key the symbols : (-) :nonactive, (+)1-2 mm, (++) 3-5 mm, (+++)6-8 mm, (++6+) 9-11 mm,

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