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Synthesis and Antimicrobial Evaluation of some 2-Azetidinone derivatives

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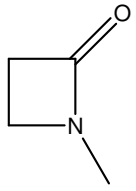
Abstract: In our present study p-anisidine is condensed with different substituted aromatic aldehydes to form respective schiff bases. The schiff bases are cyclised with chloroacetylchloride in triethylamine to yield the corresponding 2-azetidinones. Structures of synthesized compounds are confirmed by physical & spectral analysis. The compounds are evaluated for their antimicrobial properties. The activities are due to **C=O, C-N,** linkages in 2-azetidinones. All the compounds have shown comparable antimicrobial activities. Among these one 2-azetidinone having 2, 4 dimethyl amino phenyl at 2nd position have shown good activity in all the species.
Keywords:2-azetidinones, antimicrobial activity, schiff bases

Introduction

Azetidinones which are part of antibiotics structure are known to exhibit interesting biological activities. A large number of 3-chloro monocyclic β-lactam possesses powerful antibacterial, antimicrobial, anti-inflammatory, anticonvulsant & antitubercular activities. They also function as enzyme inhibitors & are effective on the central nervous system. [1-3] They are the carbonyl derivatives of azetidines containing carbonyl group at the position-2. These are also known as 2-azetidinones or more commonly β-lactam (4). Azetidinones or β-lactam chemistry is of great importance because of the use of β-lactam derivatives as antibacterial agents. [4, 5]



2-azetidinone

Cycloaddition of monochloroacetylchloride with imine (schiff base) result in formation of 2-azetidinone (β-lactam). The reaction involves direct acylation of imine with monochloroacetylchloride. The reaction is carried out with base as triethylamine gives β-lactams.[5] Although variety of drugs have been developed for treating bacterial and fungal diseases, the basic difficulty experienced with these infections are the rapid development of drug résistance to the infectious strains. Review of literature reveals that 2-azetidinones are reported to possess significant antitubercular, antibacterial & antifungal activities. P-anisidine, which is aniline derivative have been found to be biologically interesting compound for many years. Since 2-azetidinones of p-anisidine are not available, these derivatives can be done and resulting analogues are tested for their antimicrobial activity.

Experimental

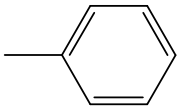
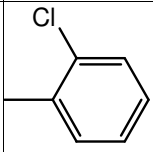
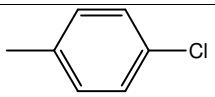
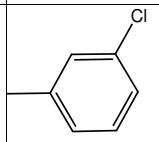
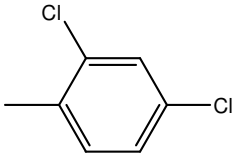
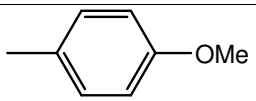
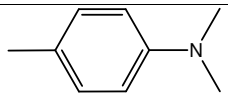
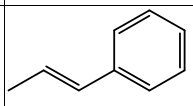
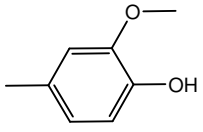
Melting points were determined in an open capillary tube using Veego VMP-1 apparatus and are uncorrected. IR spectra were recorded (in KBr) on Shimadzu FT-IR spectrometer. ^{1}H-NMR spectra was recorded on Bruker DRX-300 (300 MHz FT-NMR) using $CDCl_3$ as solvent and TMS as Internal standard. Mass spectra were recorded on Shimadzu LCMS 2010A. TLC using silica gel-G checked the purity of the compounds

1) Synthesis of Schiff Bases (2a-i):

P-anisidine (1) 0.01mol (1.23gm) was dissolved in 30ml ethanol containing few drops of glacial acetic acid. The appropriate aromatic aldehyde (0.01mol) was added to the reaction mixture. It was refluxed for 3 to 5 hours, cooled and then poured into crushed ice .The solid obtained was filtered, washed with water and crystallized with ethanol [6].

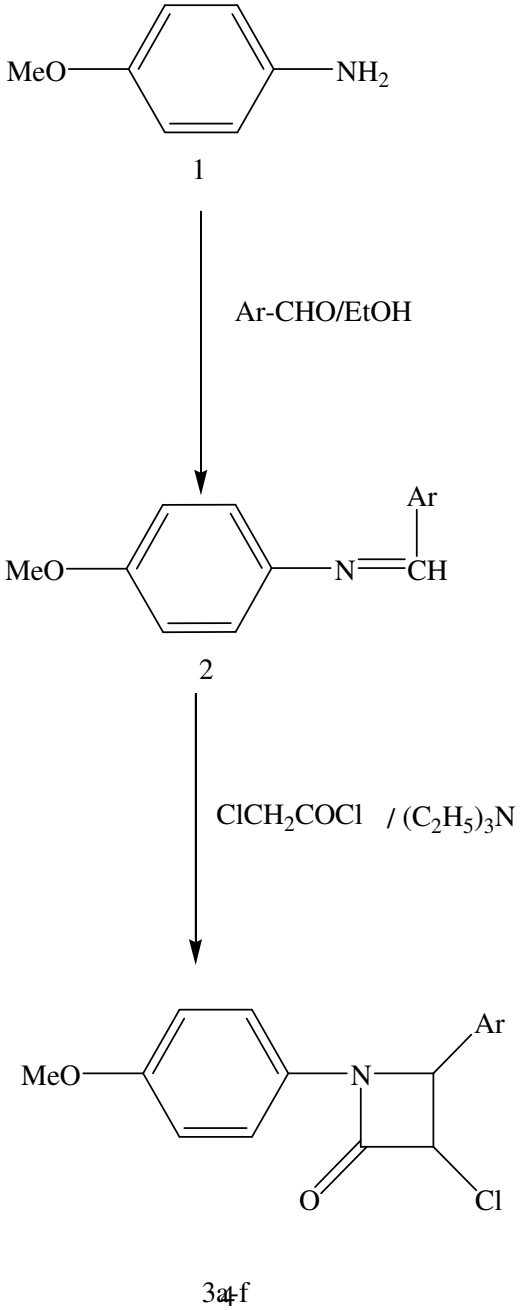
Mobile phase for TLC Benzene: Acetone 9:1

2) Synthesis of substituted 2-Azetidinones (3a-i):
To a stirred solution of substituted schiff bases of P-anisidine (2a –i) (0.01mol), triethylamine (0.02mol) in dioxan (dry 50ml) and monochloroacetylchloride (0.02mol) was added drop wise at room temperature. The reaction mixture was stirred for 30 min and then refluxed for 3 hours. A solid was obtained on removal of dioxan which was recrystallized from a mixture of ethanol/water Mobile phase for TLC Benzene: Ethanol (7:3).

COMPOUND	Ar
3a	
3b	
3c	
3d	
3e	
3f	
3g	
3h	
3i	

The physical parameters of the synthesized compounds are given in table -1.

SCHEME



3a-f

Compound No: 3c

IR (KBr, cm^{-1}): 2975.96 (Ar C-H), 1718.46 (C=O), 1475.44 (Ar C=C), 1398.30 (C-N), 1170.71(C-O), 1035.70 (ArC-O-CH_3), 806.19 (C-Cl).
^{1}H-NMR (DMSO-d_6) δ: 3.15 (s, 6H, $(OCH_3)_2$), 2.18 (d, 1H, N-CH-C), 7.32 (m, 8H, (Ar-H) $_2$), 1.4 (d, 1H, C-CH-Cl).
MS (*m/z):* M^+ calculated 322.19, found 322.95.

Compound No: 3e

IR (KBr, cm^{-1}): 2939.31 (Ar C-H), 1718.46 (C=O), 1475.44 (Ar C=C), 1398.30 (C-N), 1170 (C-O), 1035.70 (Ar C-O-CH_3), 804.26 (C-Cl).
MS (*m/z):* M^+ calculated 356.63, found 357.90.

Compound No: 3f

IR (KBr, cm^{-1}): 2939.31 (Ar C-H), 1693.38 (C=O), 1475.44 (Ar C=C), 1398.30 (C-N), 1170.71(C-O), 1035.70 (Ar C-O-CH_3), 806.19 (C-Cl).
^{1}H-NMR (DMSO-d_6) δ: 3.10 (s, 6H, $(OCH_3)_2$), 2.12 (d, 1H, N-CH-C), 7.30 (m, 8H, (Ar-H) $_2$), 1.4 (d, 1H, C-CH-Cl).
MS (*m/z):* M^+ calculated 333.77, found 333.95.

Table -1. Physical Parameters for the synthesized 2-Azetidinones

Compound No.	Molecular weight	Melting Point ^{0}C	% Yield	Rf values	Colour
3a	287.74	240-245	39	5.6	Light brown
3b	322.19	250-255	30	4.9	Pale yellow
3c	322.19	280-285	27	5.6	Pale yellow
3d	322.19	265-270	41	5.1	Pale yellow
3e	356.63	275-280	40	4.8	Light brown
3f	317.77	262-265	47	4.9	Light yellow
3g	330.81	270-272	51	4.8	Brown
3h	313.78	268-270	30	5.0	Light brown
3i	333.77	245-248	52	4.6	Pale yellow

In vitro Antimicrobial Screening [7]

The synthesized compounds were subjected to antimicrobial screening by cup plate method for zone of inhibition. The antibacterial activity was tested against various gram positive and Gram negative bacteria and anti fungal activity against various fungal stains compared with standard drug (Ampicillin and Ketoconazole) using solvent control. The results were described in the table no -2.

Table No- 2. Antimicrobial activities of Synthesized Compounds

Comp. (100µg/ml)	Zone of Inhibition (mm)					
	Gram positive		Gram negative		Anti Fungal	
	S. faecalis	*S. Aureus*	*P. aeruginosa*	*E. Coli*	*C. albicans*	*A. niger*
3 a	15	12	11	15	22	15
3 b	11	18	21	19	23	21
3 c	19	11	14	_	16	_
3 d	17	_	19	_	20	21
3 e	_	13	_	-	21	_
3 f	_	_	_	_	23	18
3 g	21	20	19	21	24	20
3 h	_	17	_	18	20	_
3 i	20	_	18	_	19	17
3 j	16	12	15	_	_	18
Std Drug (100µg/ml)	24	20	22	22	26	20
Solvent Control (DMSO)	-	-	-	-	-	-

- indicates no activity.

Results & Discussion

All the synthesized final compounds were first purified by successive recrystallization using appropriate solvents. The purity of the synthesized compounds was checked by performing thin layer chromatography and determining melting points. Then the synthesized compounds were subjected to spectral analysis such as IR, NMR and Mass Spectra to confirm the structures. All the analytical details show satisfactory results. The following peaks confirmed the formation of 2-azetidinones. The peaks at 1718-1687 cm^{-1} , 806-804 cm^{-1} ,1398.30 cm^{-1} in FTIR have shown the groups of C=O ,C- Cl, C-N in 2-azetidinones respectively. In HNMR spectra the peaks at 1.4 ppm & 2.12-2.18 ppm for C-CH-Cl, N-CH-C groups have confirmed the formation of 2-azetidinones.All the mass spectras showed the molecular ion peaks for their respective molecular weights apart from fragmentation profile.

Since our titled compounds are known to possess antimicrobial activity, the compounds were screened for their antibacterial and antifungal activity by cup-plate method. Two gram positive bacteria such as *Staphylococcus aureus* and *Streptococcus faecalis*, two gram negative bacteria such as *Escherichia coli* and *Pseudomonas aeruginosa* and two fungal species such as *Aspergillus Niger* and *Candida albicans* are tested for the activities. The concentration of 250, 500 and 750 µg/ml of our titled compounds has been used. Ampicillin and

ketoconazole have been used as standards. All the compounds have shown mild to moderate activities. Among these one 2-azetidinone having 2, 4 dimethyl amino phenyl at 2nd position **(compd no 3g)** have shown good activity in all the species.

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