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Research Article

Synthesis of Some New Azetidinones Derived from Heterocyclics and their Antimicrobial Activity

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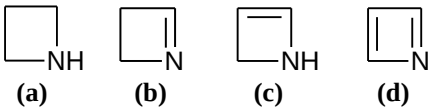
ABSTRACT

This present work deals with the synthesis, characterization and biological activity of some new Azetidinones derived from heterocyclics. Different aryloxy acetic acd were obtained from different substituted or unsubstituted phenols upon treatment with chloro acetic acid in presence of sodium hydroxide. The aryloxy acids were converted to respective acid chlorides by treating with thionyl chloride in benzene. The acid chloride was straight away used for next step. The Schiff bases were obtained by reaction of 4-amino benoic acid with substituted aldehydes in acetic acid. Then Schiff bases on reaction with acid chloride gave different azetidinones. The final derivatives of the Azetidinones were obtained by reaction with 2-amino pyridine moiety which gave different Azetidinones derivatives. The structures of the newly synthesized compounds have been established on the basis of their spectral data and elemental analysis. The synthesized compounds were screened for antimicrobial activity by paper disc diffusion method. All compounds were evaluated for antimicrobial activities against *Bacillus Pumilus, Bacillus Subtilis Staphylococcus aureus* and *Escherichia Coli.* The potency of the synthesized compounds was determined against standard drug Ciprofloxacin by measuring the zone of inhibition and calculating the MIC.

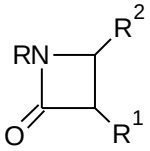
Keywords: Azetidinones, Schiff Base, Antimicrobial activity.

INTRODUCTION

Azetidin **(a),** 1-azetin **(b),** 2-azetin **(c),** and azete **(d)** are the nitrogen analogues of cyclobutane, cyclobutene and cyclobutadiene repectively. Azetidines are well studied, in particular their derivative the azetidin -2-ones (β-lactam) have received considerable attention mainly because of the antibacterial properties of penicillin and cephalosporins. The chemistry of both 1-and 2-azetidins has been comprehensively reviewed.



(a) **(b)** **(c)** **(d)**



Azetidin-2-one

Azetidin-2-one is a hydrolytically sensitive colourless solid, m.p. 73-74 ^{0}C. Other simple azetidin-2-ones are usually low melting solids or oils.[1]

Efforts have been made in exploring such new aspects of β-lactam chemistry versatile intermediates for their synthesis of aromatic β- amino acid and their derivatives, peptides, polyamines, polyamino alcohols, amino sugars and polyamino ethers. The cyclic 2-azetidinone skeleton has been extensively used as a template to build the heterocyclic structure fused to the four membered rings.

The β-lactam heterocycles are still the most prescribed antibiotics used in medicine. They are considered as an important contribution of science to humanity[2].

Azetidin-2-ones are the most extensively studied derivative of azetidin-2-one, largely as a result of the discovery of the antibacterial properties of penicillin, cephalosporin and cephamycin. Recently, there has been considerable interest in other fused β-lactam, such as claulanic acid, thienamycin and the related olivanic acid derivative and the penems. Non-fused β-lactam containing natural products include the nocardicins[3], and the monobactams[4, 5] as well as the more complex pachystermines A and B[6], wild-firetoxin[7] and the bleomycins[8].

Compounds carrying azetidin-2-one ring are reported to exhibit certain biological activities like antibacterial[9-24], antifungal[25], antiviral[26], anticancer[27], anti-inflammatory[28-29], anticonvulsant[30], hypotensive [31-33], hypnotic[34-38], antitubercular [39-42].

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- lactam.

MATERIALS AND METHODS:

*Materials:*All the chemicals and solvents were obtained from E-Merck and S.D. Fine India (AR grade) and were used without further purification.

Methodology

**Author for Correspondence*

Preparation of Aryloxy Acetic Acid (1a-f): In to a clean dry round bottomed flask a solution of phenol compound (10gm) in sodium hydroxide (33%, 35ml) was prepared by stirring. To this solution freshly prepared chloroacetic acid(50%,5ml) was added and the sodium salt that separated was dissolved by adding sufficient amount of water, the mixture was heated under reflux on a water bath for one hour. The clear solution obtained was cooled and diluted with water (10ml). It was acidified with HCL (1:1) till acidic to Congo red.

The whole solution was then extracted with ether (300ml). The ethereal layer was washed with water and then with a solution of sodium bicarbonate (5%, 250ml). The whole aqueous layer was separated and acidified with dil HCL. The precipitated aryloxy acetic acid was filtered and crystallized from water. All the aryloxy acids were prepared by using above method.

Praparation of Acid Chlorides: The aryloxy acid (0.1 moles) (1a-f) was dissolved in dry benzene (20 ml) and to this thionyl chloride (0.2 moles) was added drop by drop with occasional stirring. After completion of the addition, the whole mixture was refluxed for two hours. More benzene was added excess of thionyl chloride was completely removed. The process was repeated for 2-3 times. The acid chloride was straight away used for next step

Preparation of Schiff Base (Ia-e): The equimolar quantity of 4-amino benzoic acid and appropriate benzaldehyde were refluxed in a 100 ml round bottomed flask in 20 ml of acetic acid for 3 hours. Cooled and poured into the mixture of ice and water and collected the separated solid compound. The compound obtained was crystallized from alcohol.

Preparation of azetidin-2-ones (IIa_1-a_2),(IIb_1-b_6),(IIc_1-C_6),(IId_1-d_6),(IIe_1-e_4): The Schiff base (0.02moles) (II) was take in a 250 ml round bottomed flask and 25 ml of dry benzene (30ml) was added and stirred well to dissolve the solids. The above solution was added to the freshly prepared solution of aryloxy acid chloride in benzene (0.02 moles) in round bottomed flask with stirring. The mixture was then refluxed for six hours. After that benzene was distilled off under redused pressure. The residue upon cooling produced solid and the obtained solid was crystallized from aqueous alcohol. The physical characterization data of the prepared compounds were listed in table 1.

Preparation of azetidin-2-ones derivative ($IIIa_1$-a_2), ($IIIb_1$-b_6),($IIIc_1$-C_6),($IIId_1$-d_6),($IIIe_1$-e_4): The equimolar quantity of substituted azetidinone (0.001moles) (III) and 2-amino pyridine (0.001 moles) were refluxed in a 100 ml round bottomed flask in 25 ml of pyridine for 24 hours. The reaction mixture was cooled and poured to in the mixture of ice and water and collected the separated solid. The solid obtained was crystallized from aqueous alcohol. The physical characterization data of the prepared compounds were listed in table 2.

Antimicrobial Activity: All the compounds synthesized in the present investigation were screened for their antibacterial activity by subjecting the compound to standard procedures. Antibacterial activity was tested on nutrient agar medium against *Bacillus Pumilus, Bacillus Subtilis Staphylococcus aureus* and *Escherichia Coli* which are representative types of gram positive and gram negative organisms respectively. The antibacterial activity of the compound was assessed by disc-diffusion method.

Preparation of Nutrient Agar Media

Media composition and procedure: The nutrient agar media was prepared by using the following ingredients.

Peptone (bacteriological)	20 gm
Beef extract (Bacteriological)	5 gm
Sodium Chloride	5 gm
Agar	20 gm
Distilled water up to	1000 ml

Weighed quantities of peptone and beef extract were dissolved in distilled water by gentle warming and then specified amount of agar was dissolved by heating on water bath. Then the pH of the solution was adjusted to 7.2 to 7.4 by adding the sodium chloride and the volum of final solution was made up to 1000 ml with distilled water. Then it was transferred in to a suitable container, plugged with non-adsorbent cotton and the media was sterilized by in autoclave at 121^0 C for 20 minutes at 15 1bs pressure.

*Preparation of Test Solution: T*en mg of compound was dissolved in 10 ml of DMF. From this 1 ml of solution was taken and diluted up to 10 ml with DMF. Now the concentration of the test solution was 100µg/ml. from this 0.5 ml solution was taken and diluted up to 1ml with DMF. Now the concentration of this test solution was 50µg/ml.

Preparation of Standard Antibiotic Solution: Ciprofloxacin was used as standard antibiotics for comparison and solutions were prepared by using sterile water, as they were water-soluble. The solutions are diluted by using sterile water so that the concentrations of the solution were 100µg/ml.

Preparation of Discs: Discs of 6-7 mm in diameter were punched from NO.1 Whattmann filter paper with sterile cork borer of same size. These discs were sterilized by keeping in oven at 1400C for 60 minutes. Then standard and test solution were added to each disk and discs were air-dried.

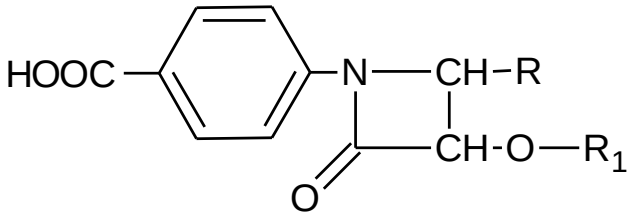
Method of Testing: The sterilized media was cooled to 45^0 C with gentle shaking to bring about uniform cooling and then inoculated with 18-24 hrs old culture under aseptic conditions, mixed well by gentle shaking. This was poured into sterile Petri dishes (properly labeled) and allowed the medium to set. After solidification all the Petri dishes were transferred to laminar flow unit. Then the discs which were previously prepared were carefully kept on the solidified media by using sterilized forceps. These Petri dishes were kept as it is for one hour diffusion at room temperature and then for incubation at 37^0 C for 24 hrs in an incubator. The extent diameter of inhibition after 24 hrs was measured as the zone of inhibition in millimeters.

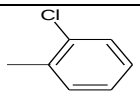
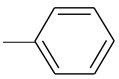
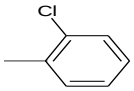
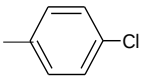
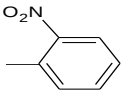
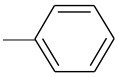
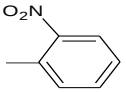
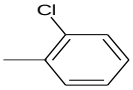
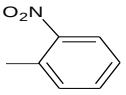
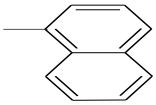
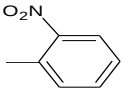
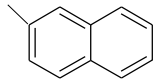
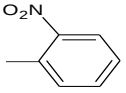
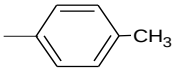
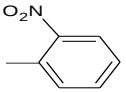
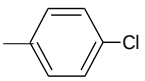
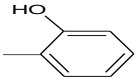
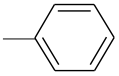
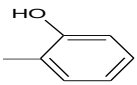
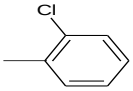
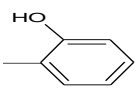
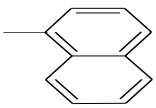
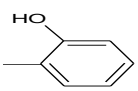
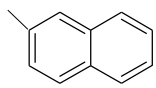
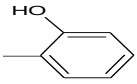
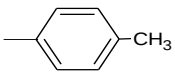
RESULTS

All the synthesized compound were screened for antibacterial activity at the concentration of 50µg/ml and 100 µg/ml using DMF as a control against staphylococcus aureus, Bacillus pumilus, bacillus subtilis and Escherichia coli by disk diffusion method on nutrient agar media.

Ciprofloxacin was used as standard drug for the comparison at the concentration of 50µg/ml and 100 µg/ml against gram positive and gram negative bacteria used for the study. The data in the table 5.5 and table 5.6 indicate that compounds IIa_1, IIb_1, IIb_2, IIb_3, IIc_5, IIc_6, IId_1, IId_4, IId_6, IIe_3 and IIe_4 from azetidinone and where as from azetidinone derivatives the compound $IIIa_1$, $IIIb_4$, $IIIc_6$, $IIId_1$, $IIId_2$, $IIId_5$ were found to possess good activity among new derivatives against both gram positive and gram negative bacteria. The remaining compound of the both the series shown weak to moderate activity.

Table 1: Characterization data of Azetidinones (IIa_1-a_2), (IIb_1-b_6), (IIc_1-c_6), (IId_1-d_6), (IIe_1-e_4)



Sr. No.	Compound Code	R	R_1	Mol. Formula	Mol. Weight	Melting Point
1	**IIa_1**			$C_{22}H_{16}O_4NCl$	479	146-150 ^{0}C
2	**IIa_2**			$C_{22}H_{15}O_4NCl_2$	447	210-212 ^{0}C
3	**IIb_1**			$C_{22}H_{16}O_6N_2$	404	180-184 ^{0}C
4	**IIb_2**			$C_{22}H_{15}O_6N_2Cl$	438	216-220 ^{0}C
5	**IIb_3**			$C_{22}H_{18}O_6N_2$	454	180-182 ^{0}C
6	**IIb_4**			$C_{22}H_{18}O_6N_2$	454	210-214 ^{0}C
7	**IIb_5**			$C_{23}H_{18}O_6N_2$	418	210-212 ^{0}C
8	**IIb_6**			$C_{22}H_{15}O_6N_2Cl$	438	210-215 ^{0}C
9	**IIc_1**			$C_{22}H_{17}O_5N$	375	166-170 ^{0}C
10	**IIc_2**			$C_{22}H_{16}O_5NCl$	409	180-184 ^{0}C
11	**IIc_3**			$C_{26}H_{19}O_5N$	425	200-202 ^{0}C
12	**IIc_4**			$C_{26}H_{19}O_5N$	425	176-180 ^{0}C
13	**IIc_5**			$C_{23}H_{19}O_5N$	389	178-180 ^{0}C

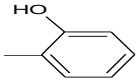
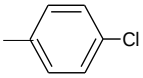
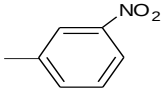
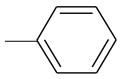
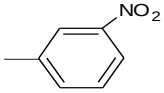
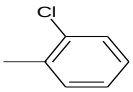
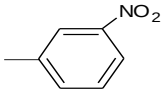
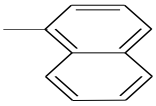
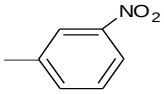
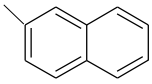
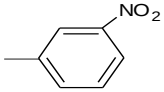
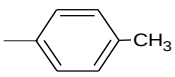
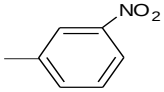
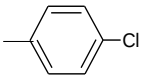
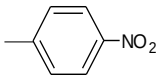
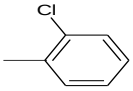
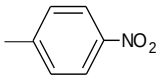
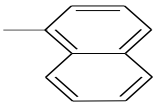
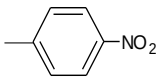
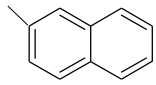
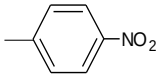
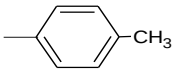
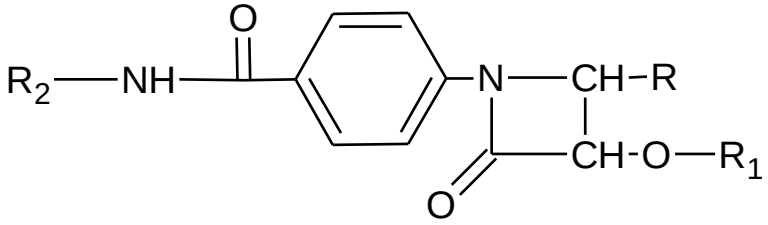
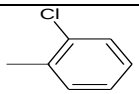
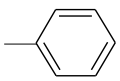
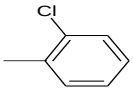
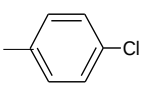
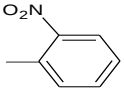
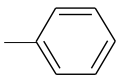
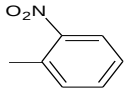
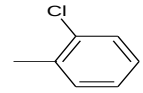
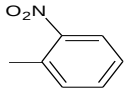
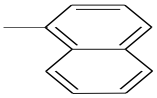
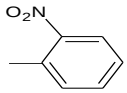
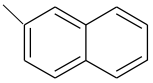
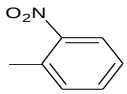
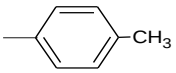
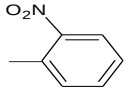
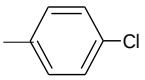
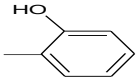
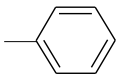
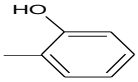
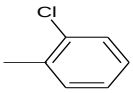
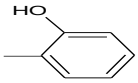
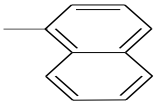
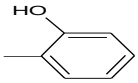
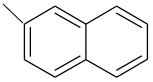
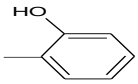
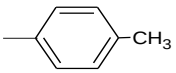
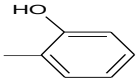
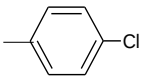
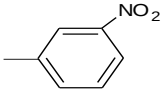
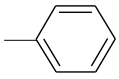
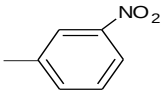
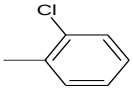
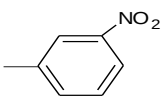
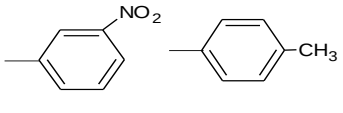
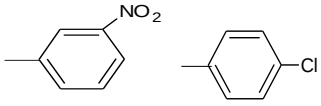
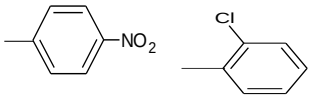
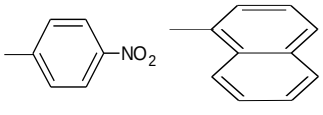
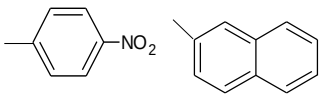
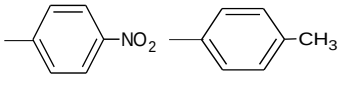
14	**IIc$_6$**			$C_{22}H_{16}O_5NCl$	409	186-190 ^{0}C
15	**IId$_1$**			$C_{22}H_{16}O_6N_2$	404	256-260 ^{0}C
16	**IId$_2$**			$C_{22}H_{15}O_4N_2Cl$	438	180-182 ^{0}C
17	**IId$_3$**			$C_{26}H_{18}O_6N_2$	454	240-242 ^{0}C
18	**IId$_4$**			$C_{26}H_{18}O_6N_2$	454	236-240 ^{0}C
19	**IId$_5$**			$C_{23}H_{18}O_6N_2$	418	166-170 ^{0}C
20	**IId$_6$**			$C_{22}H_{15}O_6N_2Cl$	438	210-215 ^{0}C
21	**IIe$_1$**			$C_{22}H_{15}O_6N_2Cl$	438	180-184 ^{0}C
22	**IIe$_2$**			$C_{26}H_{18}O_6N_2$	454	236-238 ^{0}C
23	**IIe$_3$**			$C_{26}H_{18}O_6N_2$	454	238-242 ^{0}C
24	**IIe$_4$**			$C_{26}H_{18}O_6N_2$	418	210-214 ^{0}C

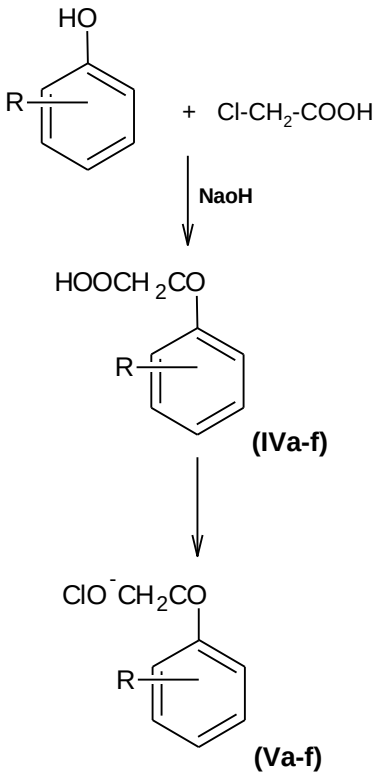
Table 2: Characterization data of Azetidinones Derivatives (IIIa$_1$-a$_2$), (IIIb$_1$-b$_6$), (IIIc$_1$-c$_6$), (IIId$_1$-d$_6$), (IIIe$_1$-e$_4$)



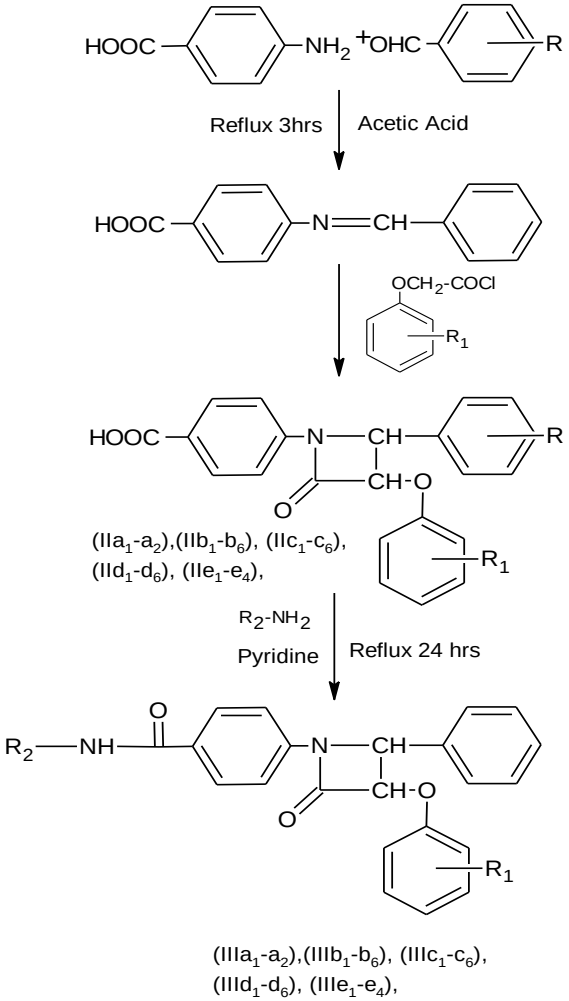
Sr. No.	Compound Code	R	R$_1$	R$_2$	Mol. Formula	Mol. Weight	Melting Point
1	**IIIa$_1$**				$C_{27}H_{21}O_3N_3Cl$	470	164-166 ^{0}C
2	**IIIa$_2$**				$C_{27}H_{20}O_3N_3Cl$	504	218-222 ^{0}C
3	**IIIb$_1$**				$C_{27}H_{21}O_5N_4$	481	209-212 ^{0}C

4	**IIIb$_2$**				$C_{27}H_{20}O_5N_4Cl$	515	182-186 ^{0}C
5	**IIIb$_3$**				$C_{31}H_{24}O_5N_4$	552	188-192 ^{0}C
6	**IIIb$_4$**				$C_{31}H_{24}O_5N_4$	552	248-252 ^{0}C
7	**IIIb$_5$**				$C_{28}H_{23}O_5N_4$	495	200-202 ^{0}C
8	**IIIb$_6$**				$C_{27}H_{20}O_5N_4Cl$	515	238-242 ^{0}C
9	**IIIc$_1$**				$C_{27}H_{22}O_4N_3$	452	166-168 ^{0}C
10	**IIIc$_2$**				$C_{27}H_{21}O_4N_3Cl$	486	218-222 ^{0}C
11	**IIIc$_3$**				$C_{31}H_{25}O_4N_3$	523	236-238 ^{0}C
12	**IIIc$_4$**				$C_{31}H_{25}O_4N_3$	523	172-176 ^{0}C
13	**IIIc$_5$**				$C_{28}H_{24}O_4N_3$	466	208-212 ^{0}C
14	**IIIc$_6$**				$C_{27}H_{21}O_4N_3Cl$	486	160-162 ^{0}C
15	**IIId$_1$**				$C_{27}H_{21}O_5N_5$	481	186-190 ^{0}C
16	**IIId$_2$**				$C_{27}H_{20}O_5N_4Cl$	515	202-206 ^{0}C
17	**IIId$_3$**				$C_{31}H_{24}O_5N_4$	552	166-168 ^{0}C
18	**IIId$_4$**				$C_{31}H_{24}O_5N_4$	552	230-232 ^{0}C

19	**IIId$_5$**		$C_{28}H_{23}O_5N_4$	495	156-158 ^{0}C
20	**IIId$_6$**		$C_{27}H_{20}O_5N_4Cl$	515	256-260 ^{0}C
21	**IIIe$_1$**		$C_{27}H_{20}O_5N_4Cl$	515	226-230 ^{0}C
22	**IIIe$_2$**		$C_{31}H_{24}O_5N_4$	552	230-232 ^{0}C
23	**IIIe$_3$**		$C_{31}H_{24}O_5N_4$	552	216-220 ^{0}C
24	**IIIe$_4$**		$C_{28}H_{23}O_5N_4$	495	198-200 ^{0}C



Scheme I



Scheme II

DISCUSSION

From the anti-bacterial screening it was found that the compound showed significant activity, some are moderate and equipotent to that of the standard employed for comparision. Hence these compounds appear to be promising anti-bacterial agents. The compounds were found to possess good activity against all the organisms used for the study. The compounds IIa_1, IIb_1, IIb_2, IIb_3, IIc_5, IIc_6, IId_1, IId_4, IId_6, IIe_3 and IIe_4 from azetidinone and where as from azetidinone derivatives the compound $IIIa_1$, $IIIb_4$, $IIIc_6$, $IIId_1$, $IIId_2$, $IIId_5$ showed good activity compared to other test compound standard ciprofloxacin, which produced maximum zone of inhibition.

CONCLUSION

The synthesized azetidinone and there derivatives shown good to moderate anti-bacterial activity. Here when the two moieties are fused and screened for anti-bacterial studies they showed a broad spectrum of antibacterial activity. They showed good activity against Gram (+ve) and Gram (-ve) bacteria.

The azetidinone molecule was responsible for antibacterial activity, but it was interesting to note that azetidinone moiety when fused with other moieties showed a broad spectrum antibacterial activity. The above results establish the fact that azetidinone moiety can be a rich source for exploitation. Therefore in search of new generation of antibiotics it may be worthwhile to explore the possibility in this area by using different moieties and increase the potency.

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