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Synthesis, QSAR and Antibacterial Activity of Some Novel Azetidinone Containing Quinoline Derivatives

M. Nagendra Babu[1*], N. Pramod[1], P. Amrutha[1], D. Kanchana[1], G.Mahaboob Basha[1], C. Gopinath[1]
1. Annamacharya College of Pharmacy, Department of Pharmaceutical Chemistry, Rajampet, Kadapa District, Andhra Pradesh, India.

ABSTRACT

The synthesis of novel azetidinone containing quinoline derivatives involves, cyclization reaction to form quinoline-3-carbaldehyde followed by Schiff's base formation and finally resulted into azetidinone derivatives as target molecules. Firstly, quinoline-3-carbaldehyde was prepared from N-phenylacetamide with $POCl_3$ in dimethyl formamide (Vilsmeyer Hacck reagent) under reflux through cyclization. The formed quinoline derivative was treated with substituted aromatic amines in presence of glacial acetic acid through grindstone process to get Schiff's bases of quinoline derivatives. Finally, these Schiff's bases were allowed to react with acetyl chloride and triethyl amine in presence of dimethyl formamide under reflux to achieve azetidinone ring formation resulting in the novel azetidinone containing quinoline derivatives. The synthesized compounds were identified by melting point and TLC as well as characterized by IR spectroscopy. The titled compounds were screened for antibacterial activity using agar well diffusion method against *Staphylococcus aureus*, *Escherichia coli*. Most of the compounds showed good antibacterial activity against G(-)ve bacteria and mild activity against G(+)ve bacteria when compared to the standard, Amoxicillin. QSAR study was performed, results revealed that the target molecules possess higher logP values which indicates that the physicochemical parameters proportional to the biological activity. Due to its high logP value the target molecules may possess CNS activities.

Keywords: Vilsmeyer Hacck reagent, quinoline derivatives, azetidinones, antibacterial activities.

*Corresponding Author Email: mennurster@gmail.com
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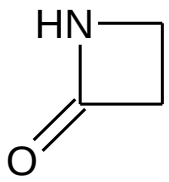
INTRODUCTION

Anti-infective chemotherapy is one of the major area in which most of the attractive antibacterial agents contain quinoline nucleus[1]. Nitrogen and oxygen containing heterocyclic compounds are one of the most extensively synthesized and screened compounds as they show most diverse pharmacological activities. Among these, chemistry of Quinoline derivatives has been of increasing interest since many of these compounds are useful as chemotherapeutic agents against malaria parasite and microbes. The chemical formula for quinoline, C_9H_7N, and it has a molecular weight of 129.15g/mol.

Quinolines and their derivatives are also important constituents of pharmacologically active synthetic compounds such as anti-inflammatory, antimicrobial agents, cytotoxic activity, antidotal and antibacterial. Quinoline and its derivatives have wide applications as drugs and pharmaceuticals and widely used as anti-malarial drugs.

The 2-Azetidinones are also known as β-lactams, are the very well known compounds belong to heterocycles. 2-azetidinone is an extremely versatile scaffold and has been present in various clinically useful drugs[2]. Due to the presence of 2-azetidinone ring, antibiotics like penicillin, carbapenem, cephalosporin, monobactums and nocardicins[3,4]. Besides its antibacterial activity[5], recently various other types of activities have been coined[6,7]. List of various activities include antitubercular[8], antifungal[9], cholesterol absorption inhibition, enzyme inhibition and anti-tumor activity. As chemotherapeutics, these drugs are being used to treat numerous microbial diseases[10-15].



2-azetidinone ring

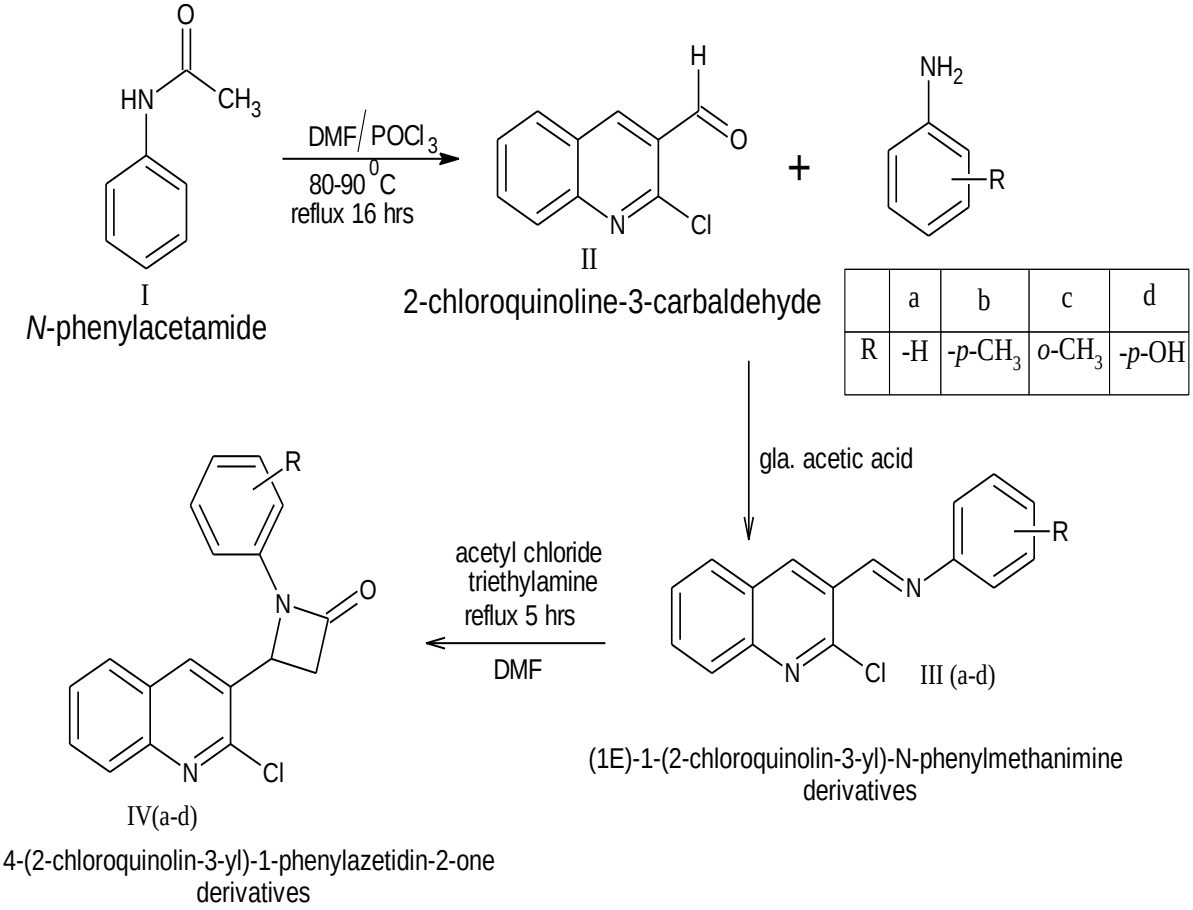
The present paper reports synthesis, characterization (using TLC and IR spectroscopy) and antibacterial screening results of 4-(2-chloroquinolin-3-yl)-1-phenylazetidin-2-one. Further research is under progress by pharmacophore modifications to study the effect of structure on antibacterial activity and CNS related activity.

MATERIALS AND METHOD

All chemicals and solvents used in this study were supplied by Merck (Darmstadt, Germany), Aldrich Chemicals Co. (Steinheim, Germany) and SD Fine Chemicals, Mumbai. Melting points

were determined in open capillaries on Digital melting point apparatus and are uncorrected. The compounds were identified by TLC and spots were visualized under UV chamber.

Experimental work



GENERAL PROCEDURE FOR SYNTHESIS OF NOVEL DERIVATIVES (1-6):

Step1; Synthesis of 2-chloroquinoline-3-carbaldehyde (II):

In a flask equipped with a drying tube, N-N dimethyl formamide (0.125 mol, 9.65 ml) was cooled to 0^0C and phosphorous oxychloride (0.35 mol, 32.2 ml) was added drop wise under stirring. To the above solution, acetanilide 0.05 mol was added and after 5 min, the solution was heated under reflux for 16 hrs at 85-90^0 C. The reaction mixture was cooled and poured into ice water and stirred for 30 min to get a yellow precipitate. It was filtered, washed with cool water, dried and re-crystallized from ethyl acetate yielding light yellow shiny needle-shaped crystals. TLC was used to monitor the completion of reaction.

Step 2: Synthesis of substituted Schiff bases of Quinolines (IIIa-d):

Place 2-chloroquinoline-3-carbaldehyde, 0.01 M (1.775 g) and aniline, 0.01 M (0.93 ml) in a mortar, add 2-3 drops of glacial acetic acid and triturate well by using pestle. Then add 5 ml of water. The crude product obtained was re-crystallized using ethanol **(IIIa)**. TLC was used to

monitor the completion of reaction. IR (KBr, cm^{-1}): 3024 (Ar-C-H), 2855 (Ar-C=C), 1144 (C-N), 1487 (C=N), 748 (C-Cl).

Place 2-chloroquinoline-3-carbaldehyde, 0.01M (1.775 g) and *p*-toulidine, 0.01 M (1.07 ml) in a mortar, add 2-3 drops of glacial acetic acid and triturate well by using pestle. Then add 5ml of water. The crude product obtained was re-crystallized using ethanol **(IIIb)**. TLC was used to monitor the completion of reaction. IR (KBr, cm^{-1}): 3026 (Ar-C-H), 2854 (Ar-C=C), 1132 (C-N), 1488 (C=N), 2923 (C-C), (750) C-Cl.

Place 2-chloroquinoline-3-carbaldehyde, 0.01 M (1.775g) and *o*-toulidine, 0.01 M (1.07 ml) in a mortar, add 2-3 drops of glacial acetic acid and triturate well by using pestle. Then add 5ml of water. The crude product obtained was re-crystallized using ethanol **(IIIc)**. TLC was used to monitor the completion of reaction. IR (KBr, cm^{-1}): 3044 (Ar-C-H), 2872 (Ar-C=C), 1132 (C-N), 1490 (C=N), 2925 (C-C), (761) C-Cl.

Place 2-chloroquinlone-3-carbaldehyde, 0.01 M (1.775g) and *p*-aminophenol, 0.01 M (1.09 ml) in a mortar, add 2-3 drops of glacial acetic acid and triturate well by using pestle. Then add 5ml of water. The crude product obtained was re-crystallized using ethanol **(IIId)**. TLC was used to monitor the completion of reaction. IR (KBr, cm^{-1}): 3044 (Ar-C-H), 2872 (Ar-C=C), 1171 (C-N), 1491 (C=N), 3410 (Ar-OH), C-Cl (760).

Step 3: Synthesis of Azetidinone containing Quinoline derivatives (IVa-d):

Equimolar mixture of four different (IIIa-d) substituted Schiff-based quinolines (0.01 M), acetyl chloride (0.01 M, 0.785 ml) and triethyl amine (0.01 M, 1.01 ml) were dissolved in dimethyl formamide (8 ml), refluxed for 5 hrs. The mixture was cooled to room temperature and poured into ice water followed by filtration and recrystallization with ethanol. TLC was used to monitor the completion of reaction. IR (KBr, cm^{-1}): 3044-3056 (Ar-C-H), 2853-2871 (Ar-C=C), 1169-1178 (C-N), 1487-1502 (C=N), 746-761(C-Cl), 3374 (Ar-OH), 2920-2923 (C-C).

ANTIBACTERIAL ACTIVITY BY AGAR WELL DIFFUSION METHOD:

Procedure:

The lyophilized forms of different strains of microorganisms like *Escherichia coli* [MTCC-2126], *Staphylococcus aureus* [MTCC-3160], were obtained from the Microbial Type Culture Collection and Gene bank (MTCC), Chandigarh, India.

Inoculation:

Single loopful of an overnight grown nutrient broth culture of each test organism served as inoculum for the antimicrobial activity determination. The average size of inoculum was about 1×10^6 cells contained in 3mm diameter of standard loop.

Determination of zone of inhibition (Agar well diffusion method)[16,17]:

In Agar well diffusion method 20 ml nutrient agar medium was poured in sterilized Petri plates (100 X15 mm) and allowed to solidify at room temperature. 24 h broth culture of test bacteria was used as inoculums under sterile conditions. The freshly prepared 100µl or 0.1ml (1×10^9 cells/ml) of organisms was set to 0.5 optical density spread with a sterile L shaped. Using cork borer several wells of 6mm in diameter were punched. To each well 100µl samples of two dilutions (1mg, 10mg) of samples were poured into wells. The Petri dishes were incubated at 37 ºC for 24hrs and the diameter of the zone of inhibition were measured in cm. Similar procedure was adopted for the pure Amoxicillin and the corresponding zone diameter were compared accordingly.

RESULTS AND DISCUSSION

The novel azetidinone containing quinoline derivatives were designed and synthesized. The synthesized derivatives were identified by melting point and thin layer chromatography and were characterized using IR spectroscopy. All the analytical details showed satisfactory results. The titled compounds were screened for their anti-bacterial activity against *Escherichia coli* [MTCC-2126], *Staphylococcus aureus* [MTCC-3160] by agar diffusion method using two concentrations 10 µg and 20 µg respectively. Amoxicillin was used as a standard.

Our studies revealed that the IVa, IVc, and IVd showed competitive zone of inhibition only on gram negative bacteria. Overall, all the compounds showed good-to-excellent antibacterial activity on gram negative species when compare with the standard, Amoxicillin than on gram positive species.

QSAR parameter study revealed that all the synthesized compounds possess logP value more than 2 and the other physicochemical parameters draws a conclusion that the target molecules may possess CNS activity also.

Table 1: Characteristic analytical data of the azetidinone containing quinoline derivatives (IVa-d):

S. No.	Compound Code	*R_f Value	Melting Point (^{0}C)	% Yield	Mol. Form.	Calculated % of Elements				
						C	H	N	O	Cl
1	Iva	0.769	155-157	50	$C_{18}H_{13}ClN_2O$	70.02	4.24	9.07	5.18	11.48
2	IVb	0.523	148-150	72	$C_{19}H_{15}ClN_2O$	70.7	4.68	8.68	4.96	10.98
3	IVc	0.717	163-164	70	$C_{19}H_{15}ClN_2O$	70.7	4.68	8.68	4.96	10.98
4	IVd	0.595	248-250	75	$C_{18}H_{13}ClN_2O_2$	66.57	4.03	8.63	9.85	10.92

* Mobile phase = Chloroform:ethanol – 9:1

Table 2: Antibacterial activity results of compounds IVa-d by Agar diffusion method:

S. No.	Bacteria	**IVa** (mm)		**IVb** (mm)		**IVc** (mm)		**IVd** (mm)		**Amoxicillin** (mm)	
		10 µg	20 µg	10 µg	20 µg	10 µg	20 µg	10 µg	20 µg	10 µg	20 µg
1	*S. aureus*	0	0.4±0.02	0	0	0	0.2±0.01	0	0.3±0.04	1.6±0.12	2.6±0.2
2	*E. coli*	1.5±0.01	2.2±0.12	0.5±0.13	1.1±0.21	1.0±0.23	2.0±0.24	1.7±0.31	2.8±0.32	1.1±0.13	1.8±0.21

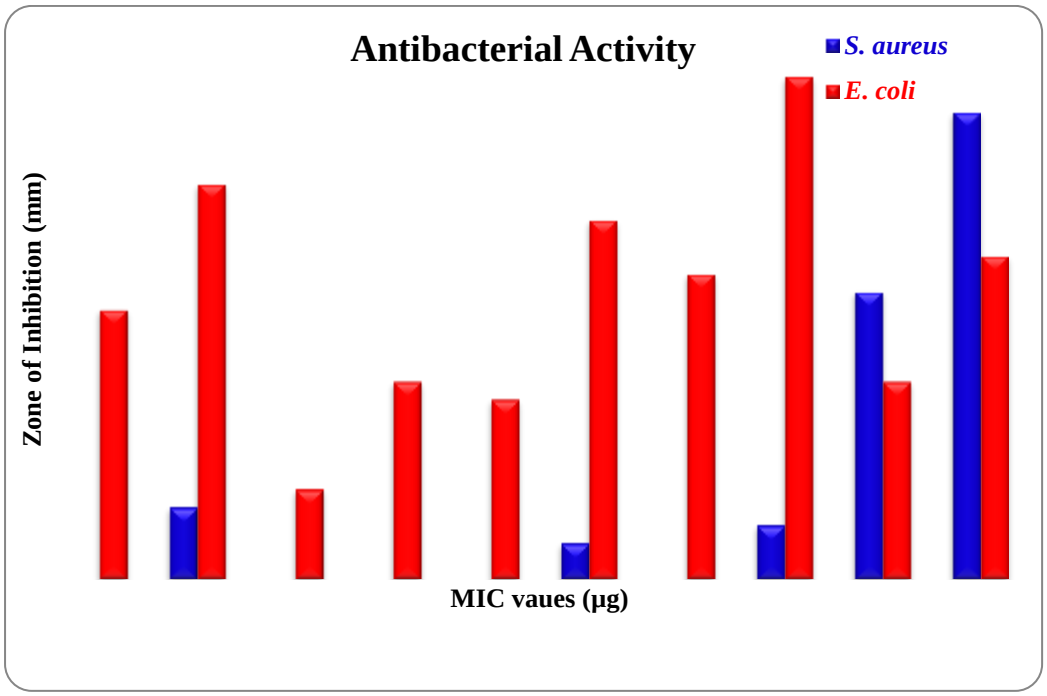


Figure 1: MIC values of titled compounds against E. coli and S. aureus at 10 µg and 20 µg

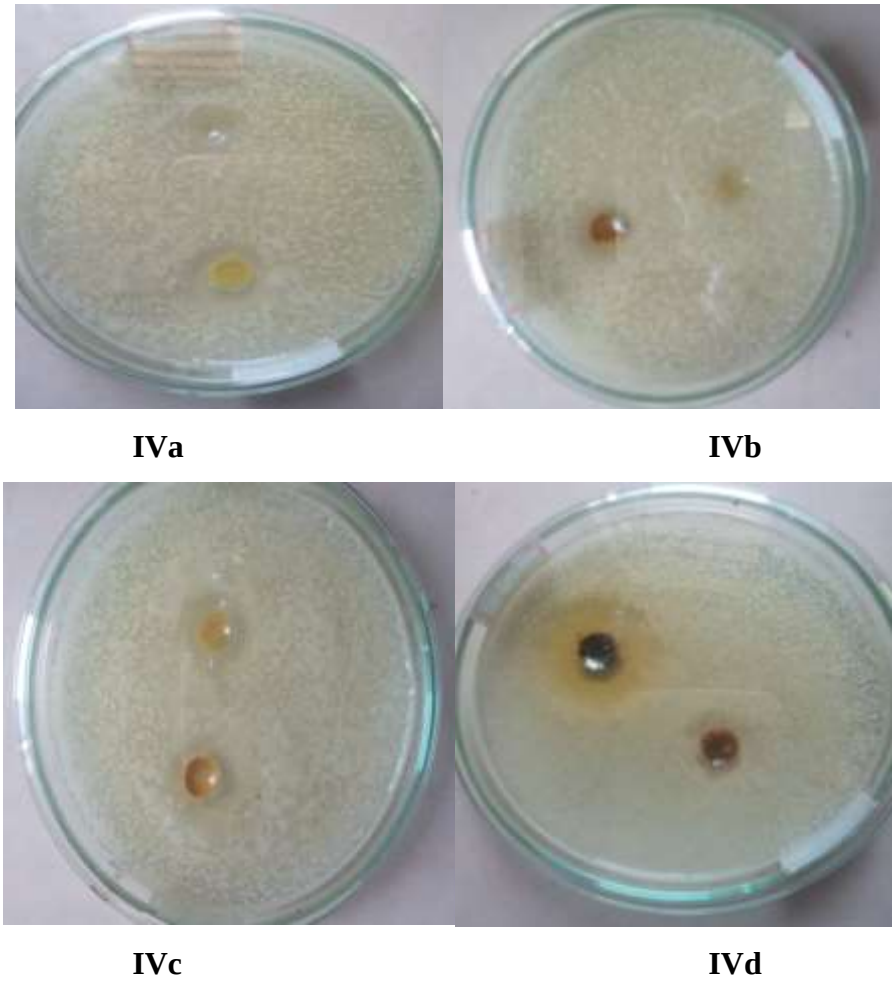


Figure 2: Zone of Inhibition of Compounds (IVa-d) against Gram Negative Bacteria *E. coli*

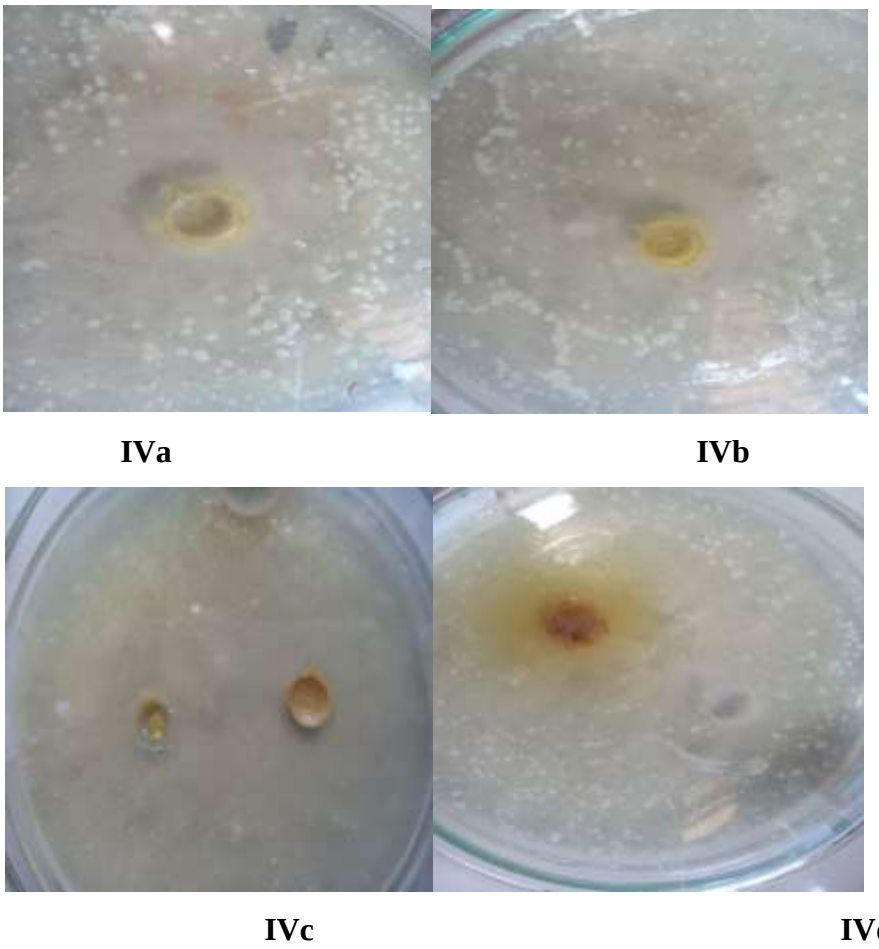


Figure 3: Zone of Inhibition of Compounds (IVa-d) against Gram Negative Bacteria *S. aureus*

Table 3: QSAR Parameters of the titled compounds:

Property	Value			
	IVa	**IVb**	**IVc**	**IVd**
Mass	308.76	322.78	322.78	324.76
LogP	3.78	4.49	4.49	3.33
H-bond acceptors	3	3	3	4
H-bond donors	0	0	0	1
Rotatable bonds	2	2	2	2
PSA	33.2	33.2	33.2	53.43
Chiral centers	1	1	1	1
Rings	4	4	4	4

CONCLUSION

All the titled compounds were synthesized and subjected to screen for their *in-vitro* antibacterial activity against *Escherichia coli* MTCC-2126 and *Staphylococcus aureus* MTCC-3160 to determine MIC values. The compounds IVa, IVc, and IVd favoured good-to-excellent gram negative antibacterial activity when compared to standard Amoxicillin which might be due to

presence of electron donating groups. Pharmacophore modifications of the derivatives may lead to further potent antibacterial agents to enhance the research scope. As per the logP values of titled compounds, these compounds may possess CNS activity too, so the research need to be carried out to know the structure activity relationship using various *in-silico* methods followed by *in-vitro* studies to study CNS related activities.

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REFERENCES

1. Desai NC, Dodiya AM. Synthesis, characterization and in vitro antimicrobial screening of quinoline nucleus containing 1,3,4-oxadiazle and 2-azetidione derivatives. J. Saudi. Chem. Soc. 2014; 18: 425-31.
2. Parul D Mehta, Sengar NPS, Pathak AK. 2-Azetidinone – A new profile of various pharmacological activities. Eur. J. Med. Chem. 2010; 45: 5541-60.
3. G.S. Singh. Recent progress in synthesis and chemistry of azetidinones. Tetrahedron 2003; 59: 7631-49.
4. Navin B. Patel, Jaymin C. Patel. Synthesis and antimicrobial activity of Schiff bases and 2-azetidinones derived from quinazolin-4(3*H*)-one. Arabian J. Chem. 2011; 4: 403-11.
5. Sharma P., Indapurkar P., Mandloi A. Antibacterial screening of N-arylamino-3-chloro-4-(4'-dimethylamino)phenyl-azetidin-2-ones. Indian J. Pharm. Sci. 1998; 60: 128-31.
6. G.S. Singh. β-Lactams in the new millennium. Part-I: monobactams and carbapenems. Mini Rev. Med. Chem. 2004; 4: 69-92.
7. G.S. Singh. β-Lactams in the new millennium. Part-II: cephems, oxacephems, penams and sulbactam. Mini Rev. Med. Chem. 2004; 4: 93-109.
8. Kagthara P, Teja S, Rajeev, D, Parekh, H.H. Synthesis of some 2- azetidinones as potential antitubercular agents. Indian J. Heterocycl. Chem. 2000; 10: 9–12.
9. Anand K. Halve, Deepti Bhadauria, R. Dubey. N/C-4 substituted azetidin-2-ones: synthesis and preliminary evaluation as new class of antimicrobial agents. Bioorg. Med. Chem. Lett. 2007; 17: 341-45.

10. E.G. Mata, M.A. Fraga, C.M.L. Delpiccolo. An efficient, stereoselective solid-phase synthesis of β-lactams using Mukaiyama's salt for the Staudinger reaction. J. Comb. Chem. 2003; 5: 208–10.
11. R.P. Pawar, N.M. Andurkar, Y.B. Vibhute. Synthesis and antimicrobial activity of Schiff bases and 4-thiazolidinones. J. Indian Chem. Soc. 1999; 76: 271–72.
12. R.F. Abdulla, K.H. Fuhr. Monocyclic antibiotic β-lactams, J. Med. Chem. 1975; 18: 625–27.
13. S.N. Maiti. Overcoming bacterial resistance: role of β-lactamase inhibitors. Top. Heterocycl. Chem. 2006; 2: 207–46.
14. C.D. Risi, G.P. Pollini, A.C. Veronese, V. Bertolasi. A new simple route for the synthesis of (±)-2-azetidinones starting from β-enaminoketoesters. Tetrahedron Lett. 1999; 4: 6995–98.
15. W. Durckheimer, J. Blumbach, R. Lattrell, K.H. Scheunemann. Recent developments in the field of β-lactam antibiotics. Angew. Chem. Int. Ed. Engl. 1985; 24: 180–202.
16. Reshma Kayarmar, G.K. Nagaraja, Prashantha Naik, H. Manjunatha, B.C. Revanasiddappa, T. Arulmoli. Synthesis and characterization of novel imidazoquinoline based 2-azetidinones as potent antimicrobial and anticancer agents. J. Saudi Chem. Soc. (2014).
17. D. Greenwood, R.C.B. Slack, J.F. Peutherer. 14th ed., Medical Microbiology, ELBS, London, 1992.