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Modern Synthetic Approaches to 2-Azetidinone Derivatives: A Review

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Abstract

2-Azetidinone, commonly known as β-lactam, is an important four-membered nitrogen-containing heterocyclic compound that has attracted considerable attention in synthetic organic and medicinal chemistry. Heterocyclic compounds play a significant role in pharmaceutical, agricultural, and biomedical research because of their diverse chemical and biological properties. The presence of the β-lactam ring in penicillin, one of the earliest antibiotics, established the importance of this structural framework in drug discovery and development. Since then, numerous 2-azetidinone derivatives have been synthesized and investigated for their potential pharmacological activities. Several derivatives have demonstrated promising antibacterial, anti-inflammatory, anticancer, antidiabetic, antitubercular, analgesic, and antiviral properties. These diverse biological activities highlight the importance of 2-azetidinone as a valuable scaffold for the development of novel therapeutic agents. The present review provides an overview of the synthesis of 2-azetidinone derivatives and their reported biological activities, emphasizing their significance in medicinal chemistry and the potential for further research and development.

keywords: 2-Azetidinone, β-Lactam, Heterocyclic Compounds, Synthetic Methods, Biological Activities, Medicinal Chemistry.

I. INTRODUCTION

Heterocyclic compounds constitute an important class of organic molecules because of their structural diversity and wide range of chemical, pharmaceutical, and biological applications. Among these compounds, 2-azetidinone has gained considerable attention in organic and medicinal chemistry due to its unique four-membered cyclic structure containing a nitrogen atom. The compound is commonly known as β-lactam because its carbonyl group is located at the β-position relative to the ring nitrogen. This structural arrangement forms the characteristic β-lactam ring, which is an essential pharmacophore in several clinically important antimicrobial agents.

The discovery of penicillin established the importance of the β-lactam ring in antibiotic research and stimulated extensive investigations into its chemical properties, synthesis, and biological significance. Subsequently, numerous β-lactam-containing antibiotics, including ampicillin, cephalosporins, carbapenems, and monobactams such as nocardicin-related compounds, have been developed or investigated. The presence of

this structural unit in diverse bioactive molecules has encouraged researchers to explore new synthetic routes and modify the β-lactam scaffold to improve its pharmacological properties.

In addition to their established importance in antibacterial drug development, 2-azetidinone derivatives have been investigated for a variety of biological activities, including anti-inflammatory, anticancer, antitubercular, antiviral, analgesic, and antidiabetic effects. Certain related compounds have also attracted interest in agricultural and other applied chemical research. Their biological potential depends on the nature and position of substituents attached to the β-lactam ring, as well as on the overall molecular structure. Consequently, the development of efficient and selective synthetic methodologies remains an important area of research in heterocyclic chemistry.

The present review focuses on the synthetic approaches used for the preparation of 2-azetidinone derivatives and summarizes relevant findings reported in the scientific literature. Information from research articles and review publications in organic chemistry, medicinal chemistry, and pharmaceutical sciences is considered to provide an overview of established synthetic strategies and their relevance to biological investigations. The review aims to highlight the importance of the β-lactam scaffold, discuss its synthetic versatility, and identify opportunities for further research into novel derivatives with potentially useful biological properties.

II. REVIEW OF RELATED LITERATURE

The synthesis of 2-azetidinone derivatives has attracted considerable interest among researchers worldwide owing to their diverse applications in pharmaceutical, medicinal, and agricultural sciences. Several synthetic approaches have been reported in the literature using different starting materials, reagents, catalysts, and reaction conditions. These methods provide opportunities to develop structurally diverse β-lactam derivatives with potentially significant biological properties.

The present review summarizes previously reported synthetic methodologies for the preparation of 2-azetidinone derivatives. Particular emphasis is given to the selection of starting materials, reaction mechanisms, experimental conditions, and synthetic strategies employed by different researchers. This comparative overview provides an understanding of the available methods and their applications in the development of novel β-lactam compounds.

III. SIGNIFICANCE OF THE REVIEW

The primary objective of this review is to provide researchers with a comprehensive understanding of the different synthetic methodologies used for the preparation of 2-azetidinone derivatives. It highlights the advantages, limitations, and variations associated with different synthetic procedures.

Furthermore, this review may assist researchers in identifying previously investigated synthetic pathways, avoiding unnecessary duplication of reported work, and selecting appropriate starting materials and reaction conditions for future investigations. The collected information can also serve as a valuable reference for designing new 2-azetidinone derivatives and exploring their potential biological activities.

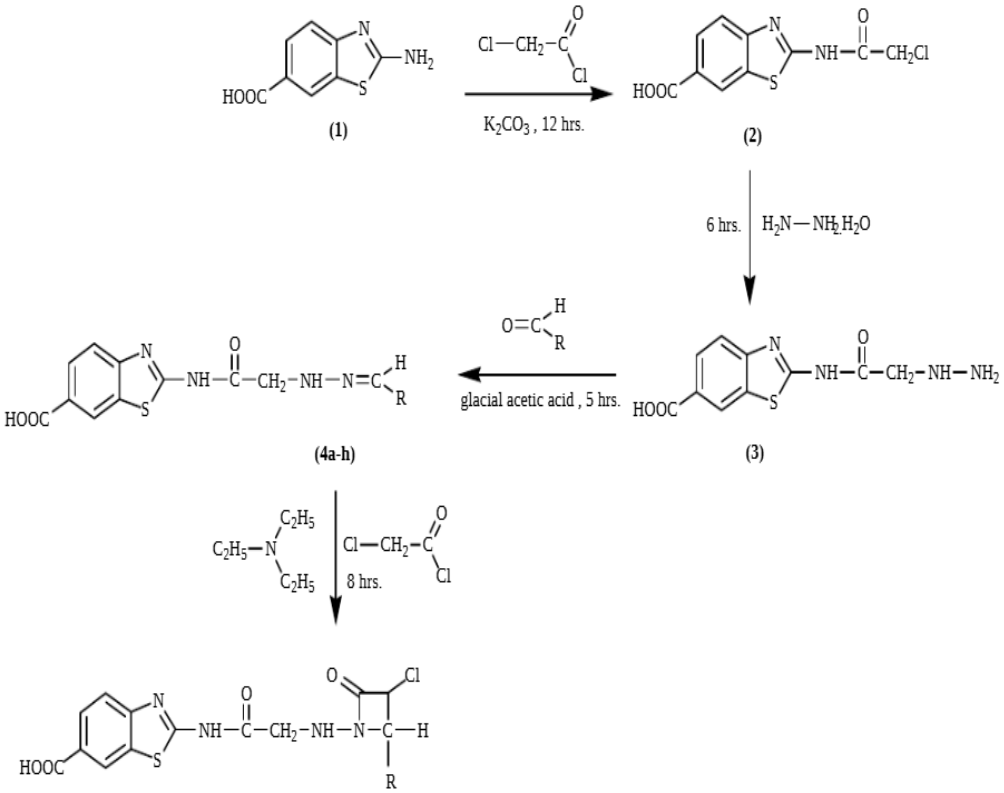
IV. SYNTHETIC METHODOLOGY

4.1 Synthesis of 2-Azetidinone Derivatives

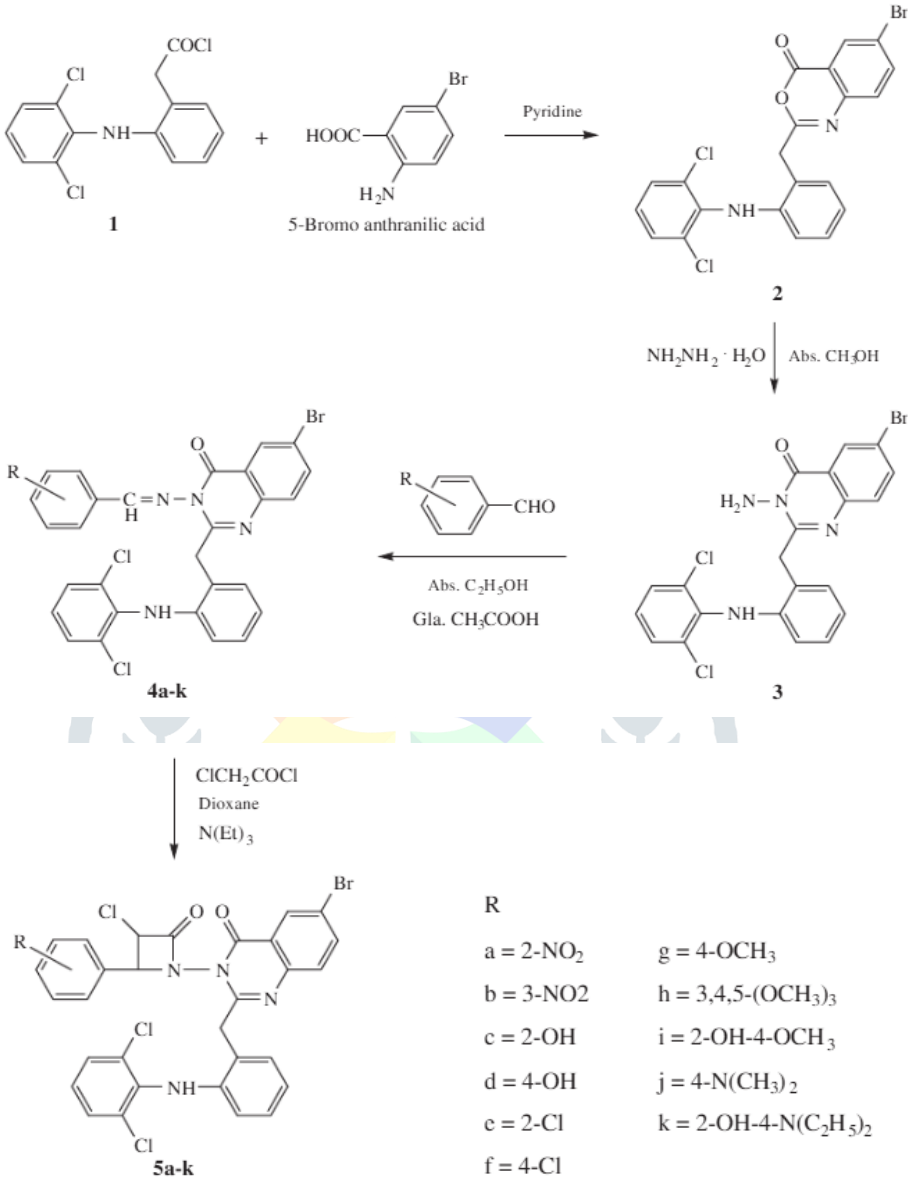
Various synthetic approaches have been developed for the preparation of 2-azetidinone derivatives. Among these, the cycloaddition of chloroacetyl chloride to Schiff bases is an important method for constructing the four-membered β-lactam ring.

According to the procedure reported by Ameya A. Chavan and Nandini R. Pai [1] 2-Aminobenzothiazole-6-carboxylic acid (1), on condensation with chloroacetyl chloride yielded 2-(2-chloroacetylamino) benzothiazole-6-carboxylic acid (2), which on amination with hydrazine hydrate yielded in turn 2-(2-hydrazino acetylamino) benzo-thiazole-6-carboxylic acid (3). Compound 3, on condensation with various aromatic aldehydes afforded a series of 2-{2-[N'-(arylidene) hydrazino] acetylamino} benzothiazole-

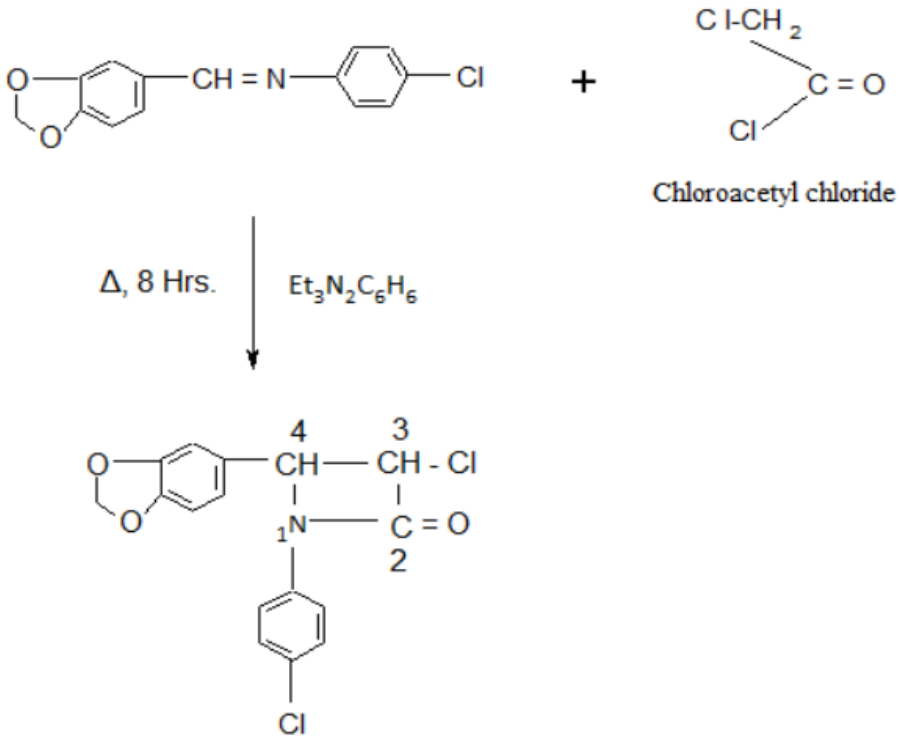
6-carboxylic acids 4a-h, which upon dehydrative annulation in the presence of chloroacetyl chloride and triethylamine yielded 2-{2-[3-chloro-2-(aryl)-4-oxoazetidin-1-ylamino]-acetylamino} benzothiazole-6-carboxylic acids.



Navin B. Patel*, Jaymin C. Patel [2] synthesized a series of 2-oxo-azetidinyl-quinazolin-4(3H)-ones 5a–k have been synthesized from
Schiff bases 4a–k. Schiff bases were synthesized by condensation reaction of compound 3 with substituted aromatic aldehydes. The benzoxazinone 2 was prepared by the cyclization reaction of acid chloride 1 with 5-bromo anthranilic acid. Further reaction of benzoxazinone 2 with hydrazine hydrate yielded compound



According to synthesis procedure reported by S.D.tarale and S.B.Shinde [3]
Synthesis of N-(4-Chlorophenyl)-4-(3,4-methylenedioxyphenyl)-3-chloro-2-azetidinone was prepared by A mixture of 3,4-methylenedioxyphenylidine-4′-chloroaniline (0.01 M) and chloroacetyl chloride (0.01 M) was dissolved in benzene (20 mL) in the presence of triethylamine (2 mL). The reaction mixture was refluxed for 8 hours and subsequently allowed to cool to room temperature, resulting in the formation of a sticky mass. The solvent was removed by evaporation using a hot water bath. The crude product was triturated with petroleum ether and purified by crystallization from 40% ethanol to obtain the corresponding N-(4-chlorophenyl)-4-(3,4-methylenedioxyphenyl)-3-chloro-2-azetidinone.

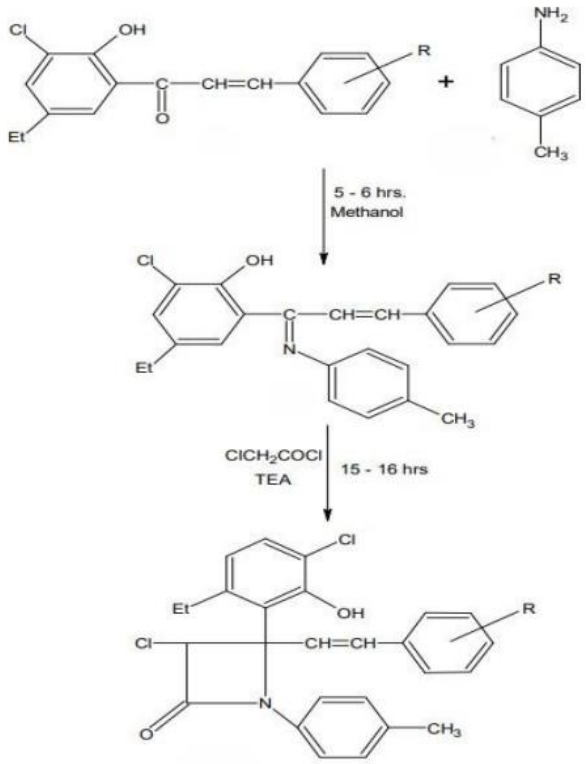


According to the procedure reported by K. Vashi et al. [4], chalcone-derived starting material and p-toluidine were used for the synthesis of Schiff base intermediates. Initially, the selected starting materials were mixed in methanol and subjected to reflux for approximately six hours to facilitate Schiff base formation.

In the subsequent step, the isolated Schiff base was dissolved in benzene, followed by the addition of triethylamine. Chloroacetyl chloride was then added dropwise to the reaction mixture under controlled conditions. The reaction mixture was further refluxed to promote intramolecular cyclization and formation of the corresponding 2-azetidinone derivative.

This synthetic transformation involves the formation of a four-membered β-lactam ring through the reaction of the Schiff base with chloroacetyl chloride. The resulting product can be further characterized using suitable analytical and spectroscopic techniques.

The reported approach demonstrates the utility of Schiff base intermediates in the synthesis of substituted 2-azetidinone derivatives and provides a useful synthetic strategy for further investigations in heterocyclic and medicinal chemistry.



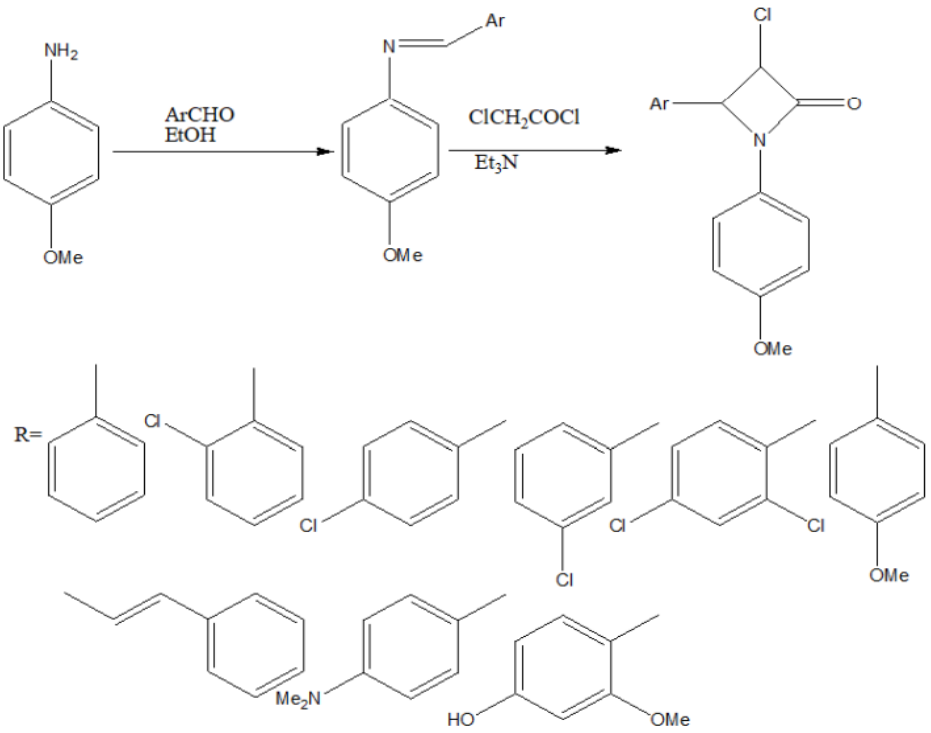
R = p-H, p-Cl, 2,4-$(Cl)_2$, o-OH, p-OH, p-CH_3, m-NO_2, o-OCH_3, p-OCH_3, p-$N(CH_3)_2$.

S. Jubie et al. [5] reported a synthetic approach for the preparation of 2-azetidinone derivatives involving the formation of Schiff base intermediates followed by β-lactam ring cyclization.

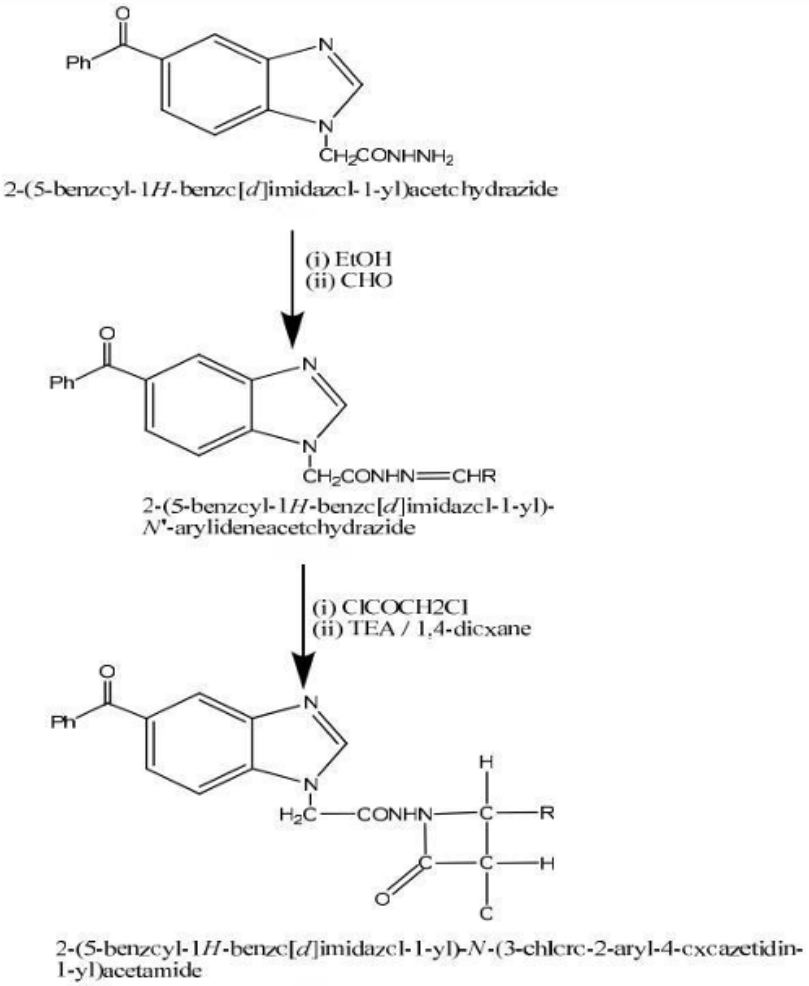
Initially, anisidine was dissolved in ethanol, and a few drops of glacial acetic acid were added to the reaction mixture. Subsequently, an appropriate aromatic aldehyde was introduced, and the resulting mixture was heated under reflux for approximately five hours to facilitate the condensation reaction and formation of the corresponding Schiff base.

In the next step, the synthesized Schiff base was dissolved in dioxane. Triethylamine was added to the solution, followed by the gradual and dropwise addition of chloroacetyl chloride. The reaction mixture was then stirred and heated under reflux to promote cyclization, resulting in the formation of the corresponding substituted 2-azetidinone derivatives.

This synthetic procedure demonstrates the application of Schiff base intermediates in β-lactam ring formation through ketene–imine cycloaddition. The method provides an alternative approach for synthesizing substituted 2-azetidinone derivatives using aromatic aldehydes and anisidine as starting materials.



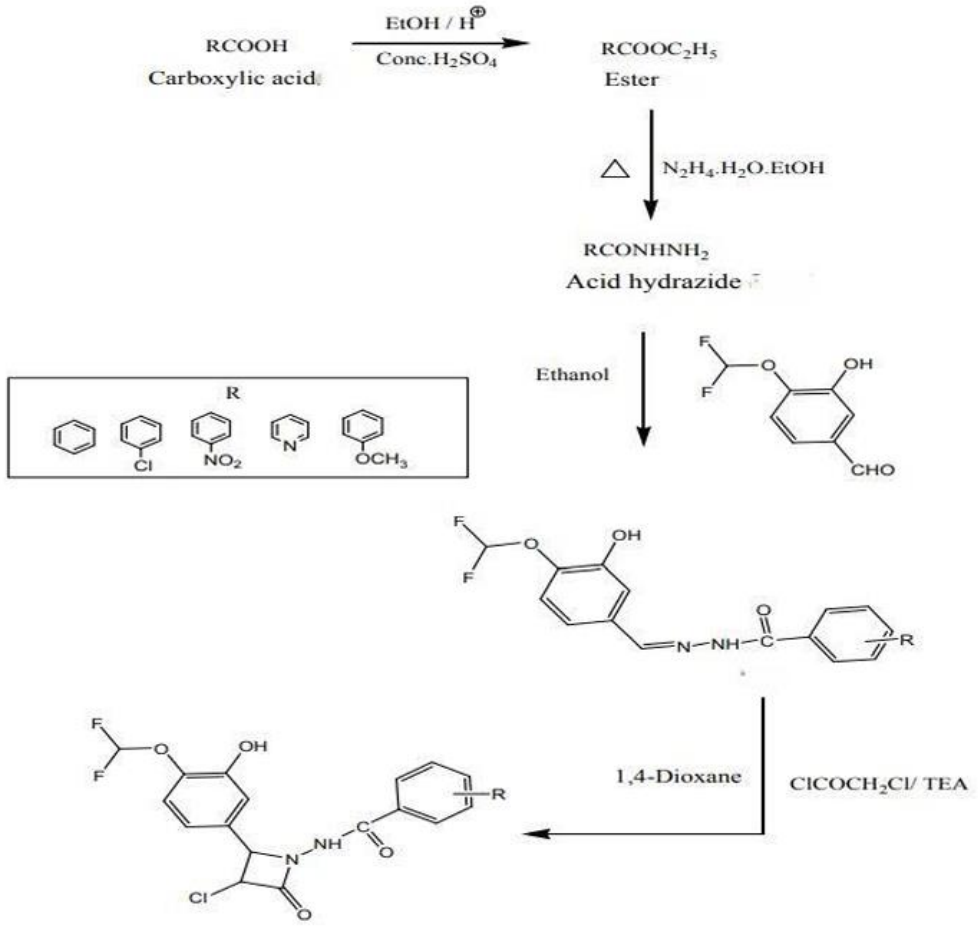
Synthesis of 2-azetidinones was done by D. Kumar et al [6] for testing its bioactivities. They reacted an acethydrazide with aromatic aldehyde in ethanol and refluxed for 2 hours to yield Schiff base. The Schiff base is then treated with trietyhyamine and chloroacetyl chloride in dioxane with constant stirring for 3 hours to yield 2-azetidinone.



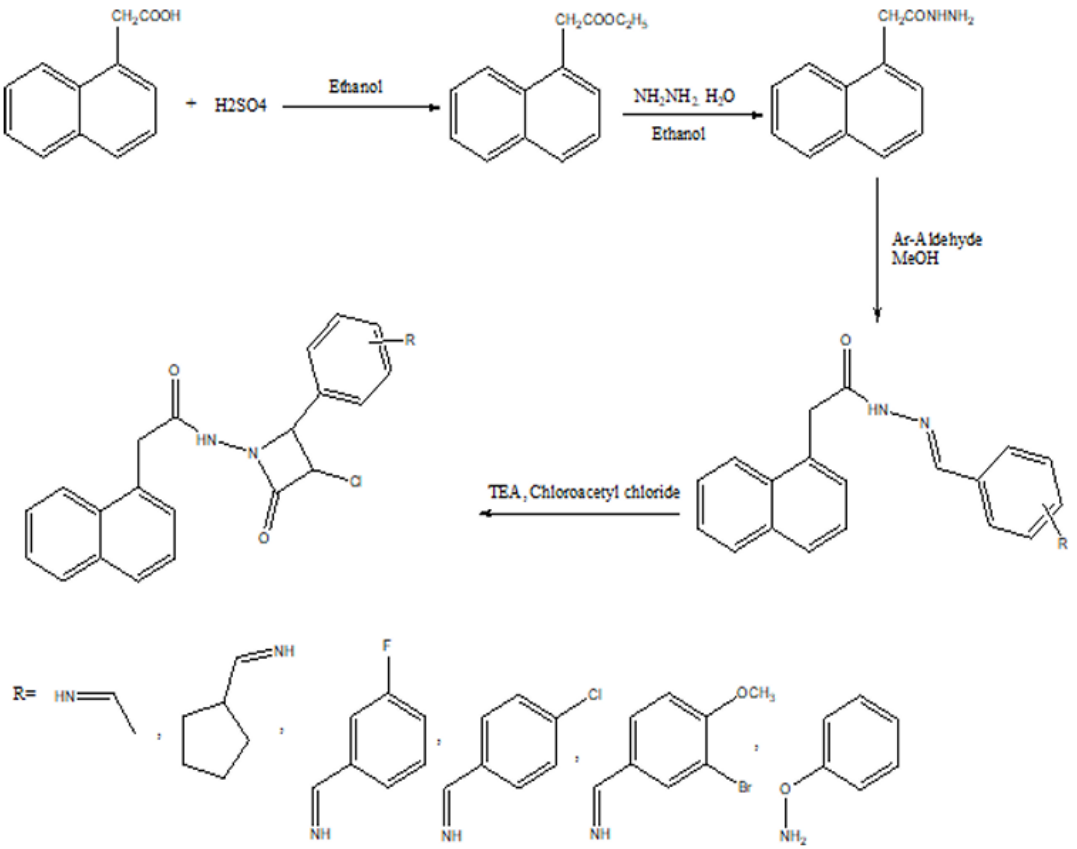
Scheme - 1

Where, R = (a) C_6H_5 (b) 4-OCH_3-C_6H_4 (c) 4-OH-C_6H_4
(d) 2-OH-C_6H_4 (e) 4-CH_3-C_6H_4 (f) 3,4-CH_2O_2-C_6H_4
(g) 4-OH-3-OCH_3-C_6H_3 (h) 3,4-C_2H_5-C_6H_4

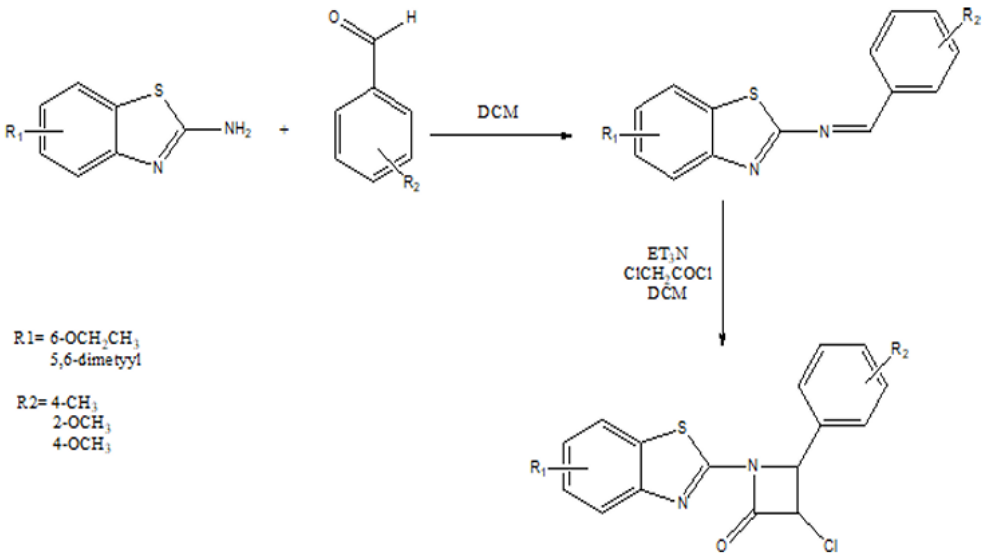
2-azetidinone derivatives were synthesized by R. M. Sulthana et al [7] using carboxylic acid as a starting material. The carboxylic acid was mixed with ethanol and conc. Sulphuric acid and then refluxed to yield an ester. This ester is then reacted with hydrazine in the presence of ethanol to form an acid hydrazide which is further reacted with aldehyde to give the Schiff base. The Schiff base is then reacted with triethylamine and chloroacetyl chloride to give 2-azetidinone.



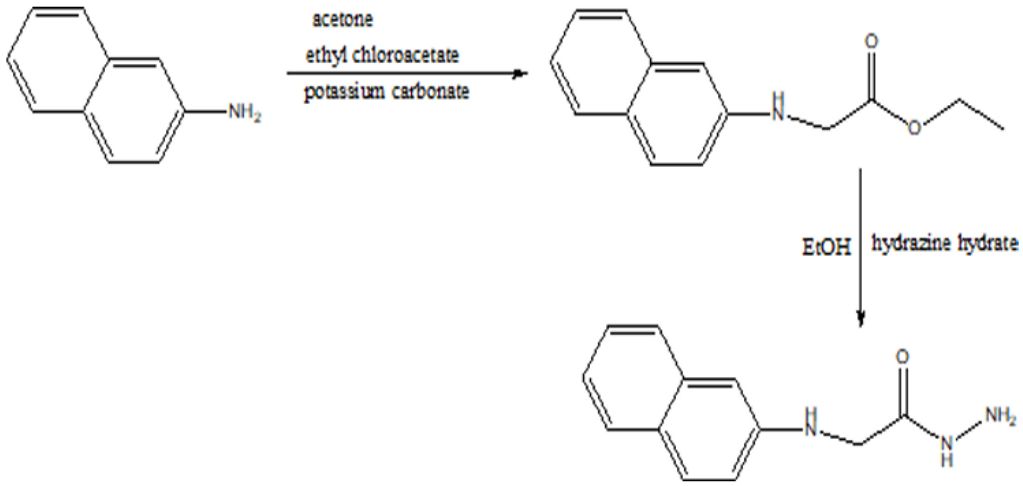
G. Subramanian et al [8] used naphthalene-1-yl acetic acid to synthesize 2-azetidinone. First this acetic acid was mixed with ethanol with drop wise addition of sulfuric acid and refluxed to give the acetate. The acetate is then dissolved in methanol and reacted with hydrazine to yield aceto hydrazide which is then reacted with aromatic aldehyde inmethanol to give a Schiff base. This Schiff base is then reacted with triethylamine and chloroacetylchloride drop wise addition to yield 2-azetidinone.

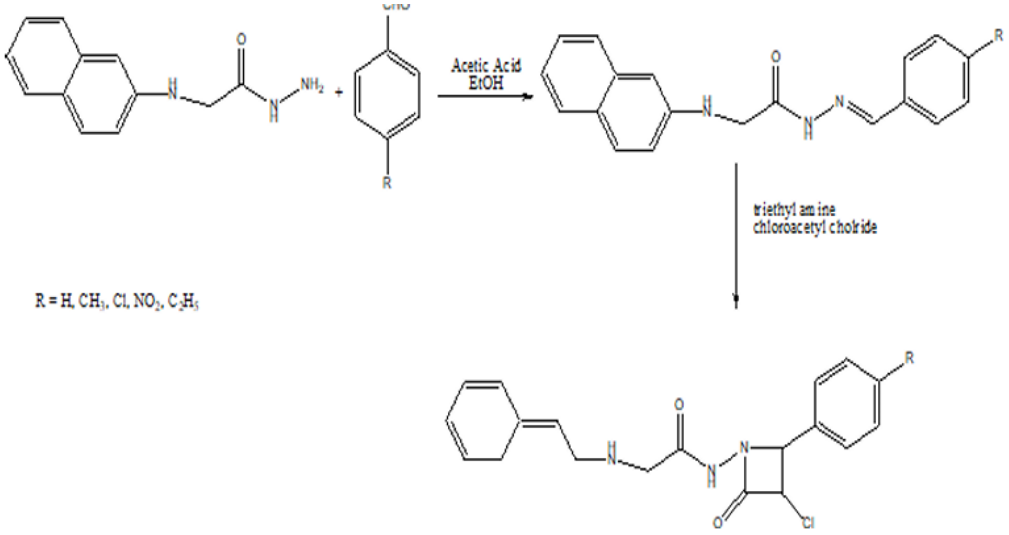


H. C. Sakarya et al [9] first prepared schiffs base by refluxing the mixture of 6-ethoxy-2-aminobenzothiazole and para- methyl benzaldehyde in dichloromethane for 6 hours to yield the precipitate of schiffs base. Chloroacetyl chloride is then added drop by drop in the mixture of dichloromethane and triethyl amine solution within the time interval of thirty minutes at cold condition and stirred. To this cold well-stirred solution Schiff base is added and stirred for nine hours and kept at room temperature for 6 hours. This reaction mixture was then extracted using NaHCO3, HCl, and brine and then purified by column chromatography over silica gel to get 2-Azetidinones.

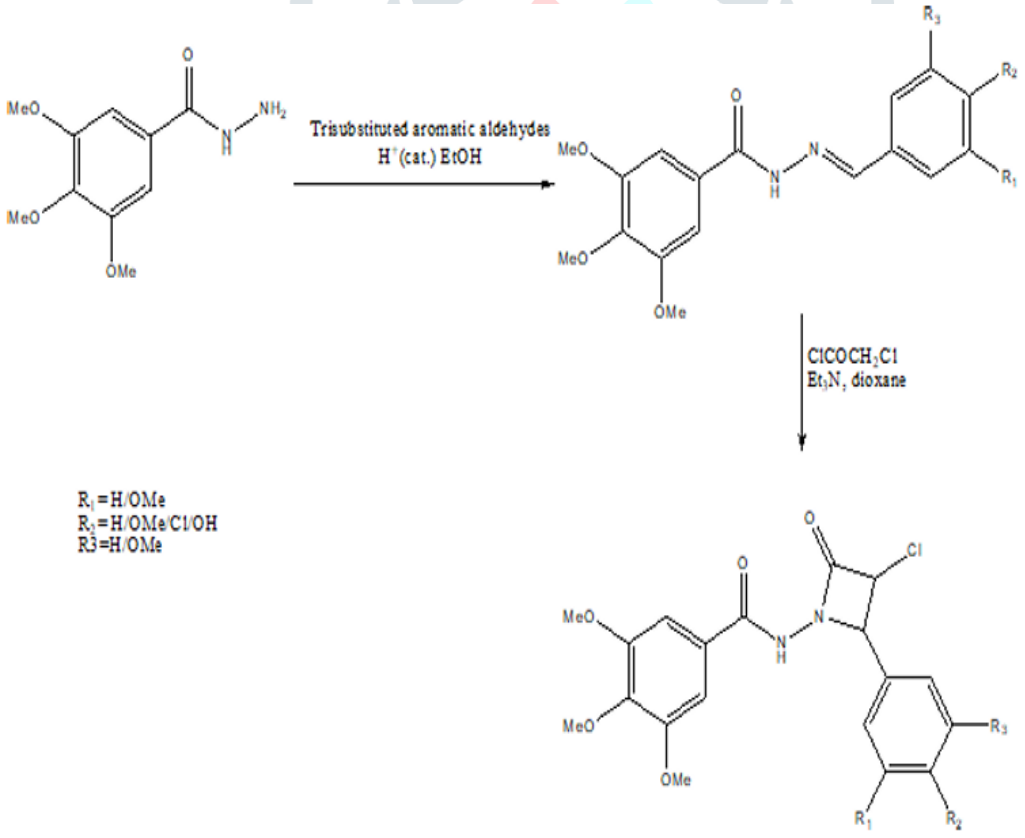


G. Kumar et al [10] first mixed naphthaline-2-amine with acetone and then ethyl chloroacetate was added with a pinch of potassium carbonate and stirred for 30 minutes and refluxed to yield acetohydrazide. This acetohydrazide is then mixed with ethyl alcohol and then hydrazine hydrate is slowly added to it with shaking to produce acetohydrazide. The so formed acetohydrazide is then mixed with arylaldehyde and few drops of acetic acid are added to it contained in ethyl alcohol and then refluxed to yield Schiff's base. This Schiff base is then mixed with triethyl amine and chloroacetyl chloride is then added drop wise to yield 2-azetidinone derivatives.





Synthesis of 2- derivatives using substituted hydrazides was proceeded by first treating the hydrazides with aromatic substituted aldehydes in ethanol with acidic condition to prepare Schiff bases. These Schiff bases were then dissolved in dioxane then the mixture was sequentially and gradually added with triethylamine and chloro acetyl chloride, then stirred heated to yield 2-azetidinone derivatives as shown in the reaction schemes below by N. B. Ayrim et al [11].



V. CONCLUSION AND FUTURE PERSPECTIVES

The present review highlights the significance of 2-azetidinone, also known as the β-lactam nucleus, as an important heterocyclic scaffold in medicinal and pharmaceutical chemistry. A comprehensive overview of the reported synthetic approaches and diverse applications reveals its considerable potential in the development of biologically active compounds. The presence of the β-lactam ring plays a significant role in imparting various pharmacological properties, making it an attractive structural framework for drug discovery and

development. Furthermore, this review provides valuable insights into the synthesis, structural modifications, and biological importance of 2-azetidinone derivatives. Future research may focus on developing novel derivatives, optimizing synthetic methodologies, and evaluating their pharmacological activities to identify promising therapeutic candidates. Thus, the present review may serve as a useful reference for researchers working in heterocyclic chemistry, medicinal chemistry, and pharmaceutical sciences.

Conflict of Interest: The author declares no conflict of interest.

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REFERENCES

1.Ameya A. Chavan and Nandini R. Pai,2007. "Synthesis and Biological Activity of N-Substituted-3-chloro-2-azetidinones" Molecules 12, 2467-2477

2. Navin B. Patel*, Jaymin C. Patel 2010 "Synthesis and antimicrobial activity of Schiff bases and 2-azetidinones derived from quinazolin-4(3*H*)-one" Arabic Journal of Chemistry 4 (4); 403-411

3.S.D. Tarale and R.B.Shinde "synthesis, characterization and biological activities of 2- azetidinone derivatives" © 2020 JETIR December 2020, Volume 7, Issue 12

4. K. Vashi and H. B. Naik., "Synthesis of Novel Schiff Base and Azetidinone Derivatives and their Antibacterial Activity", E-Journal of Chemistry Vol. 1, pp.272-276, 2004.

5.S. Jubie, B. Gowramma, N. K. Muthal, R. Kalirajan, S. Gomathi and K. Elango., "Synthesis and Antimicrobial Evaluation of some 2- Azetidinone derivatives", International Journal of ChemTech Research Vol.1, pp.153-157, 2009.

6. D. Kumar, F. B. Bux, and A. Singh., "Synthesis and biological activity of azetidinone", Rasayan J. Chem. Vol.3, pp.497 -502 2010.

7.R. M. Sulthana, S. D. Quine., "Synthesis, characterization, antibacterial evaluation and molecular docking studies of 2-azetidinone derivatives as novel DNA gyrase inhibitors", International Letters of Chemistry, Physics and Astronomy, Vol. 47, pp.94 -108, 2015.

8. G. Subramanian, J. Chand, S, Jupudi, P. Prudviraj., "Synthesis and Biological Evaluation of the Selected Naphthalene Substituted Azetidinone Derivatives Targeting Parkinson's Disease", Ind. J. Pharm. Edu. Vol.57, pp.552-558, 2023. 10.M. M. Aftan, M. Q. Jabbar, A. H. Dalaf, H. K. Salih., "Application of biological activity of oxazepine and 2-azetidinone compounds and study of their liquid crystalline behavior", Published by Elsevier B.V. Vol.43, pp.2040-2050, 2021.

9. H. C. Sakarya, A. Ketrez., "Synthesis of Novel cis-2-Azetidinones from Imines and Chloroacetyl Chloride Using Triethylamine", Acta Chim. Slov. Vol. 70, pp.628–633, 2023

10. G. Kumar, I. Singh, S. K. Bhatt, Nancy, Nitin, D. K. Gautam, A. Soam., "Synthesis, Characterization and In Silico Studies Of Novel Substituted Azetidinone, Substituted Thiazolidinone Containing Naphthalene Moiety, With Their Biological Activity. Educational Administration", Theory and Practice. Vol. 30, pp.1619-1628, 2024.

11. N. B. Ayrim, A. A. Balakit, S. J. Laftaa, F. F. Alkazazz, Y. Bekkar, L. Bourougaa, and B. A. Saleh., "Design, Synthesis, and Molecular Docking Studies of 2-Azetidinone-Based Combretastatin A-4 Analogues with Anticancer Activity", European Chemical Society Chemistry select Vol. 10, pp.1-12, 2025.