Recent Synthetic Developments for Functionalized Azetidinones and Thiazolidinones

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ABSTRACT

The chemistry of azetidinone and thiazolidinones is a promising field. Numerous methods for the synthesis of azetidinone and thiazolidinones and also their varied reactions offer massive scope in medicinal chemistry field. The utility of azetidinone and thiazolidinone as basic motif for various biologically potent compounds has given impetus to their comprehensive studies. This article aims to review the research work and study reported on the chemistry and medicinal importance of thiazolidinones and azetidinone during past few years.

Keywords: Azetidinone, Thiazolidinones, Chemistry, Biological activities.

INTRODUCTION

Azetidinone is commonly known as β-lactam which is a four membered cyclic amide. The first β-lactam was synthesized by Hermann Staudinger by reaction of the Schiff base with diphenylketene in a [2+2] cycloaddition reaction [55]. The four membered β-lactam nucleus with diverse substituent's tend to give profound effect on its medicinal properties. The 2-azetitinone (β -lactams) ring is a common structural motif of a number of β-lactam antibiotics which includes penicillins, carbapenems, cephalosporins and monobactams. [1,5]. Apart from this antibiotic character, a number of medicinal applications are reported for 2-azetitinone (β -lactams) scaffold such as anti-inflammatory [6], human leukocyte elastase inhibitory [16], anticancer activity [31], antitumor [23], Enzyme Inhibitors [15], anti-tubercular[12] and cholesterol absorption inhibitors activity[48].

Thiazolidinones are the analogues of thiazolidine with a carbonyl group at the fourth position belong to an important group of heterocyclic scaffolds that contain nitrogen and sulfur in a five member ring. A lot of research work on thiazolidinones has been done in the past few years. The thiazolidinones nucleus is known to be a wonder nucleus, as due to its functional diversities it posses almost all types of biological activities. This is a fundamental motif in various medicinal drugs displaying a broad spectrum of biological properties such as antimycobacterial [20, 27], antimicrobial [17, 42, 49], anticancer [26, 37], anticonvulsant [24, 40], antiparasitic [45], anti-inflammatory and analgesic [44], antidiabetic [57], anti-HIV [43], antihypertensive [47] and antifungal agents [19]. The substituted thiazolidine moiety has attracted considerable interest in the synthesis and development of biologically active compounds.

Literature survey

Ishwar k. Bhat and his team [25] have synthesized azetidinones derivatives starting with para-anisidine moiety. The synthesized compounds were screened for antibacterial and antibiotics activities. Some of them found to have better antibacterial activities than the standard ampicillin (Scheme 1).

S. J. Wadher and team [52] developed synthesis of 4- thiazolidinones from Schiff bases of amino salicylic acid. The compounds were evaluated against their antibacterial activity (Scheme 2).

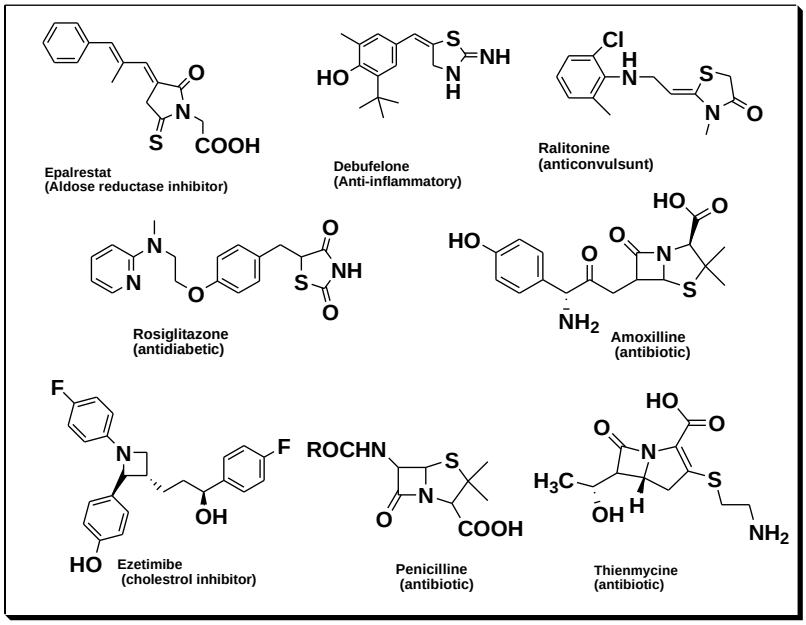
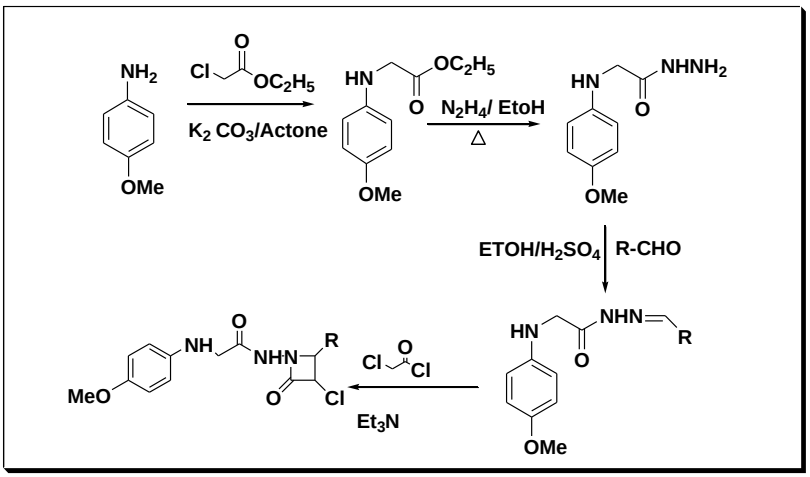
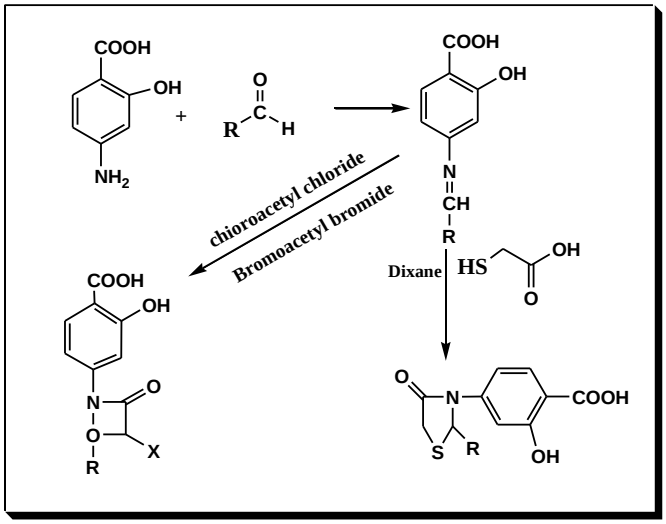


Figure 1: Drugs containing azetidinone & thiazolidinones nucleu

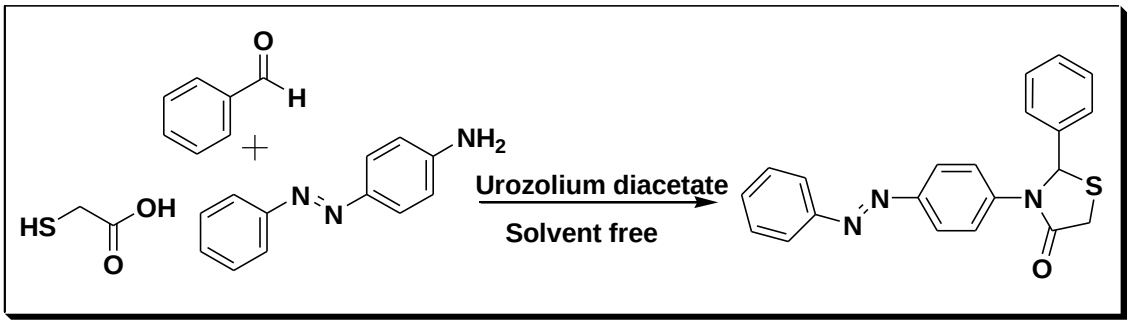


Scheme 1



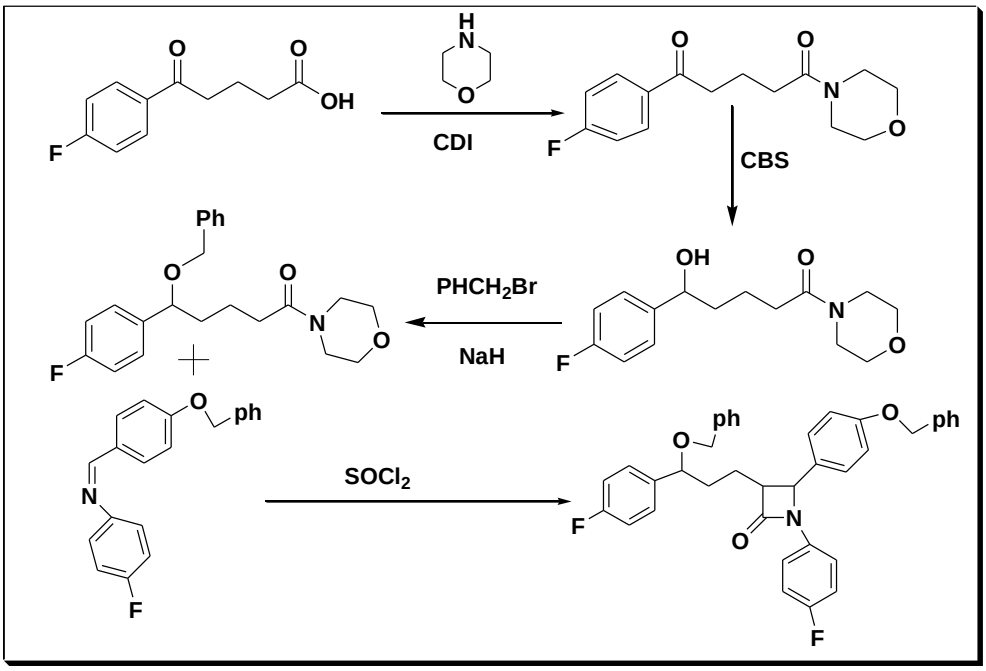
Scheme 2

Leila Zare Fekri and team [32] developed synthesis of new derivatives of 1,3-thiazolidine-4-ones from azo dispersive dyes family catalyzed by urazolium diacetate using a multicomponent reaction under solvent-free condition. This developed method has many advantages as: high yields, short reaction times, environmental friendliness, solvent-free conditions and easy workup (Scheme 3).



Scheme 3

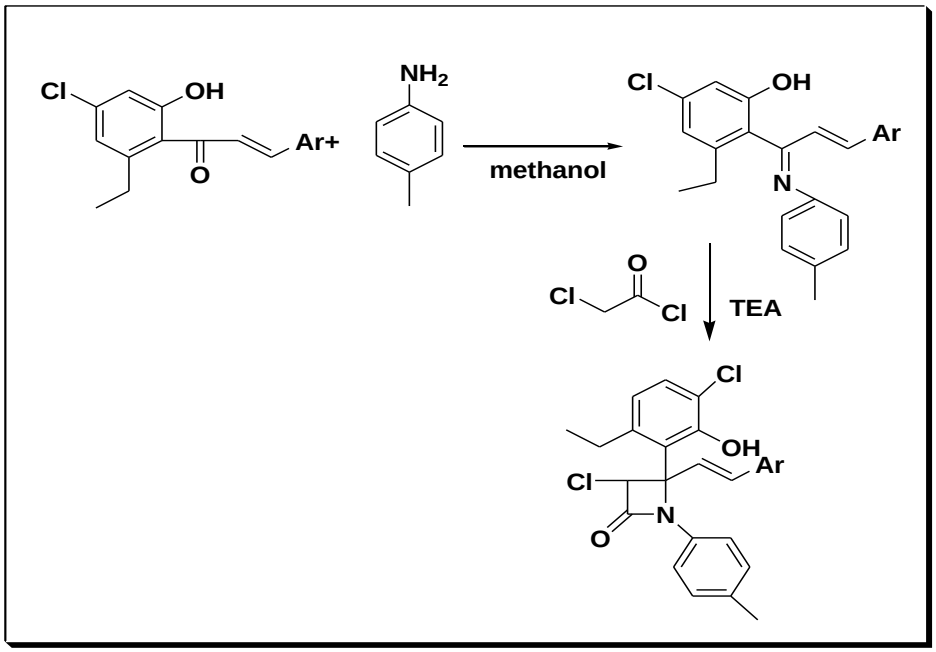
Mangesh. S. Sawant and team [33] have developed synthesis of azetidinones using chemoselective protecting group like benzyl bromideiodide and also asymemtric chiral auxillary (CBS) reagent (Scheme 4).



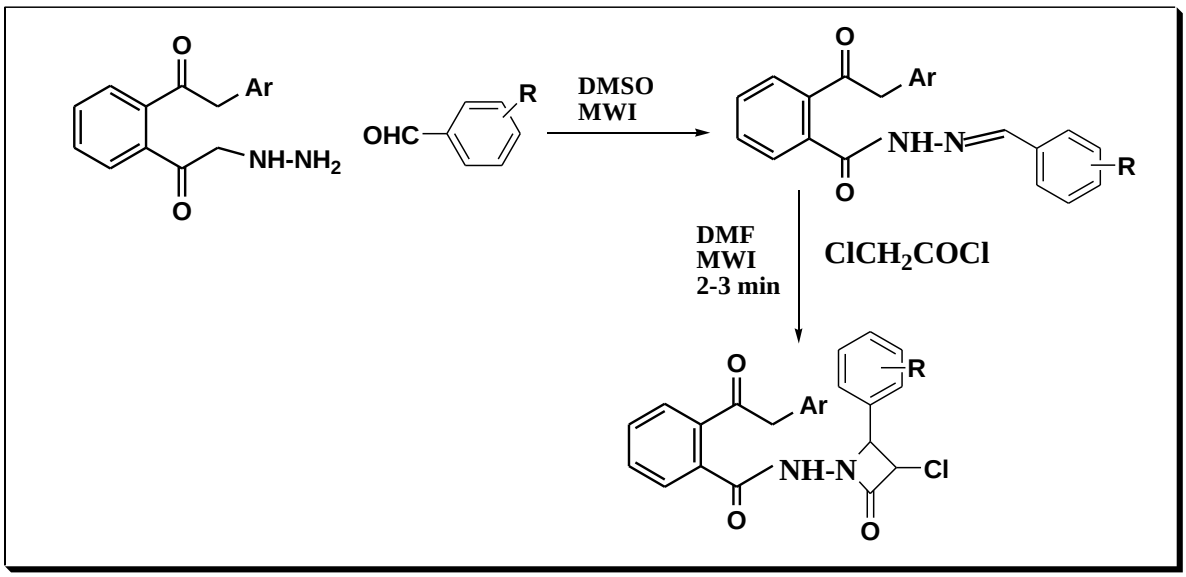
Scheme 4

Kamal vashi and coworkers [58] synthesized novel azetidinone from various schiff base derivatives prepared by the condensation of p-toluidine with different substituted chalone derivatives. The synthesized derivatives were screened for their antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* microorganisms (Scheme 5).

Smita.K. and her team [30] synthesized azetidinones derivatives starting with 2-(phenylacetyl) benzohy- drazide moiety by microware method. The synthesized derivatives have been screened against anti bacterial and anti-fungal activities and shows moderate to good results (Scheme 6).



Scheme 5

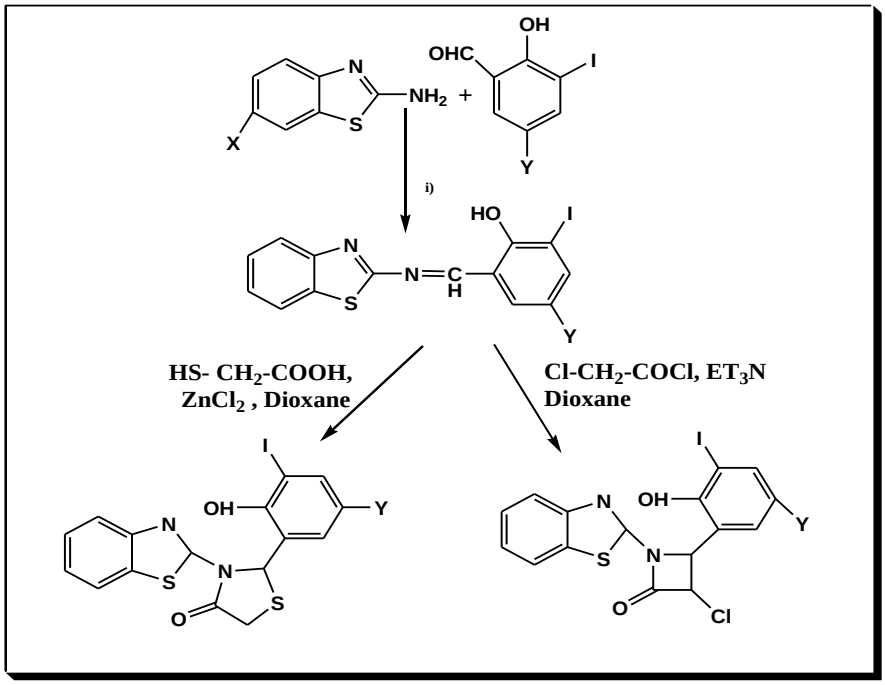


Scheme 6

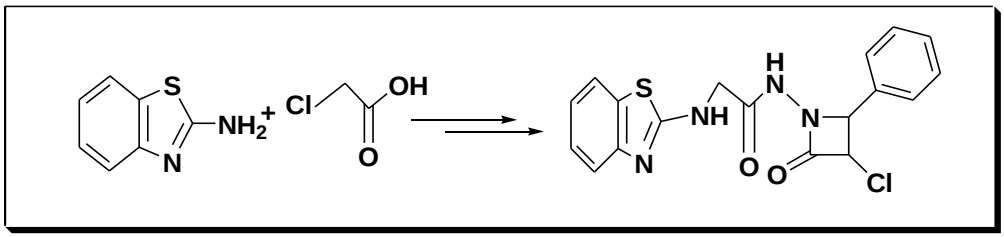
S.R. Bhvsare coworkers [54] synthesized 4- thiazolidinones and 2- azetidinones from Schiff bases of thiazole and also screened their antibacterial and antifungal activities (Scheme 7).

Kushal M Kapadiya and team [29] synthesized benzathiazole derivatives coupled with substituted azetidinone ring and was verified activity against breast tumors (Scheme 8).

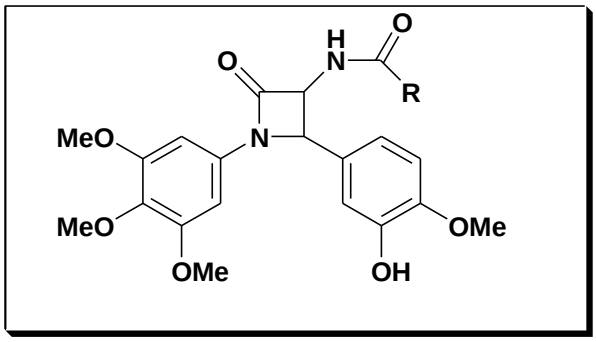
Farida Tripodi and team [22] synthesized various new derivatives of amino-2-azetidinone and tested for their anti-proliferative activity against the colon cancer SW-48 cell line. The cyclization reaction to get the 3-aminoazetidinone ring is found to be highly diastereoselective and gave a *trans* biologically active isomer under mild reaction conditions with maximum yields (Scheme 9).



Scheme 7

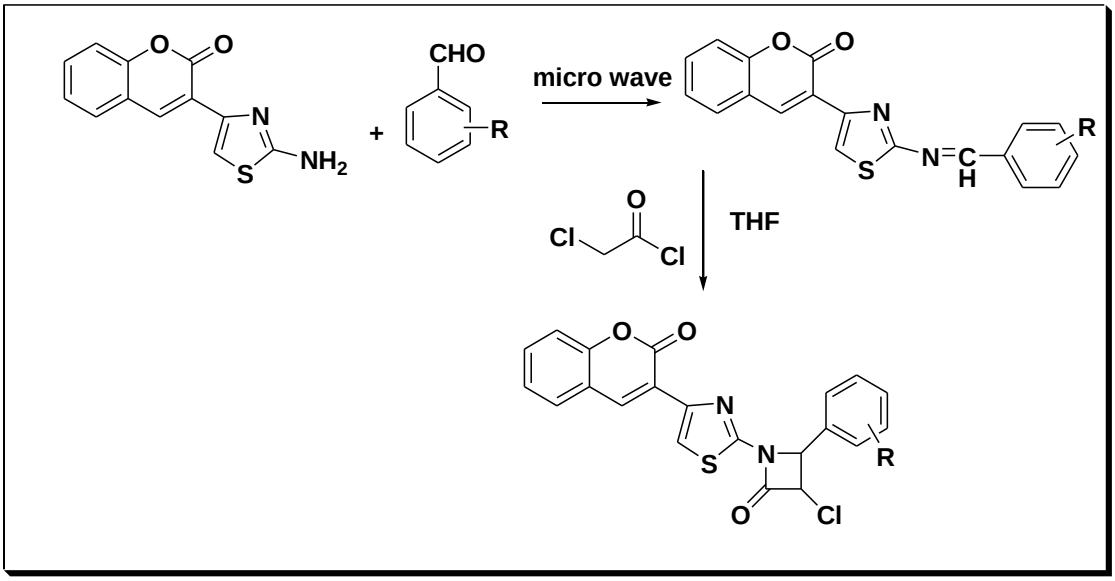


Scheme 8



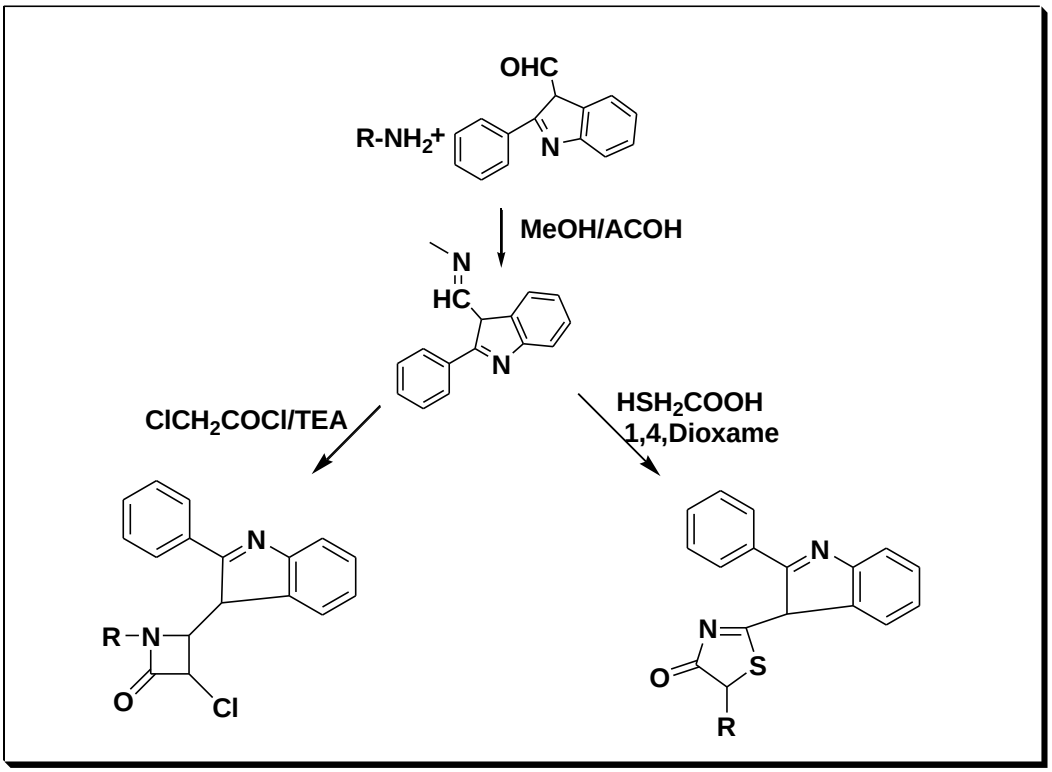
Scheme 9

Bhanvesh Naik and team [14] developed a novel approach for the rapid & efficient synthesis of Schiff bases of coumarine coupled aminothiazole under microwave conditions and these Schiff bases cyclized to azitidione ring. The newly synthesized derivatives have been screened for their antibacterial and antifungal activities (Scheme 10).



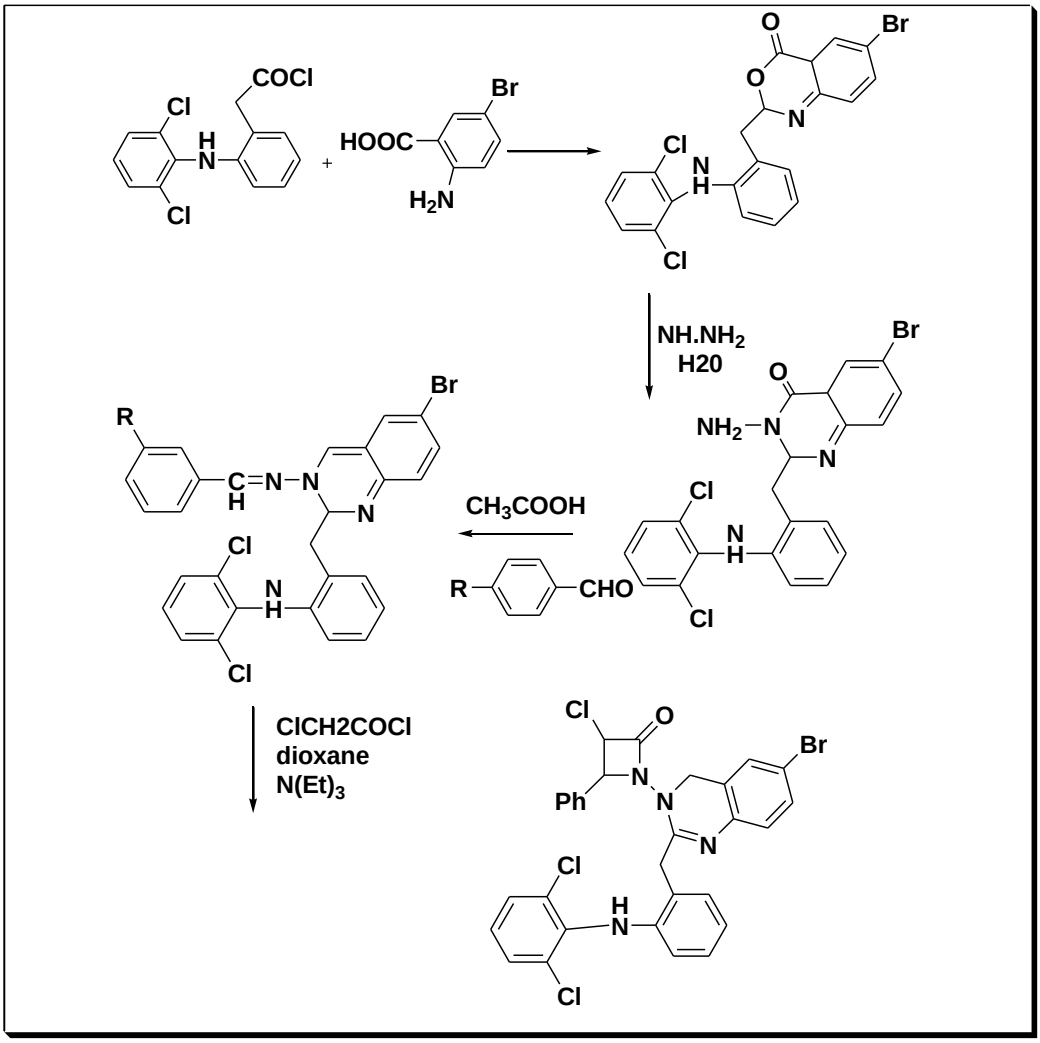
Scheme 10

Archana and her team [9] reported synthesis of newer substituted azetidinones & thiazolidinone derivatives as potent anticonvulsant agent with reported the yield of 63 to 67 %. The synthesized derivatives were in vivo screened for their anticonvulsant and acute toxicity activity in MES and PTZ models. Almost all synthesized compounds have shown promising anticonvulsant activity (Scheme 11).



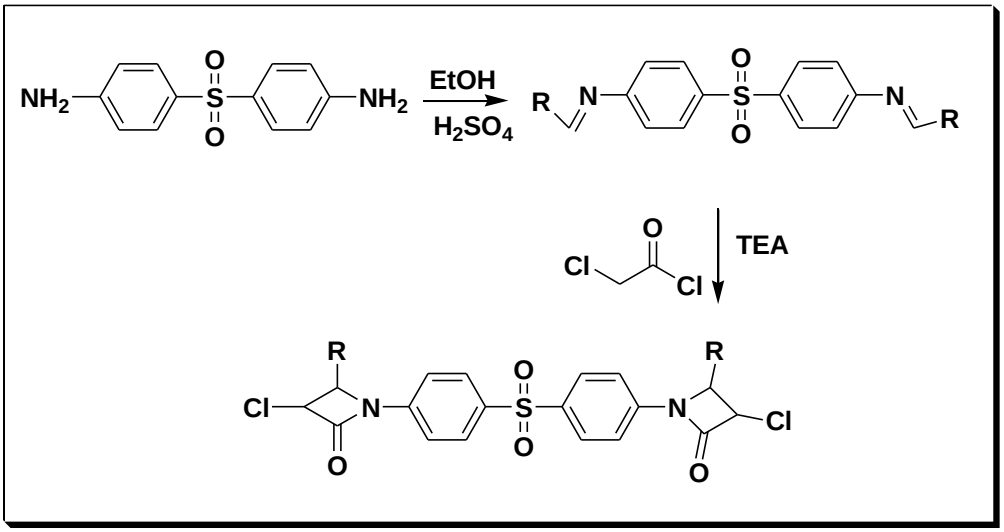
Scheme 11

Navin B. and team [36] synthesized 2-azetidinones derived from quinazolin-4(3H)-one and performed their antibacterial and antifungal activities in vitro. It was revealed that compounds having chloro and methoxy group exhibited good antimicrobial activity (Scheme 12).



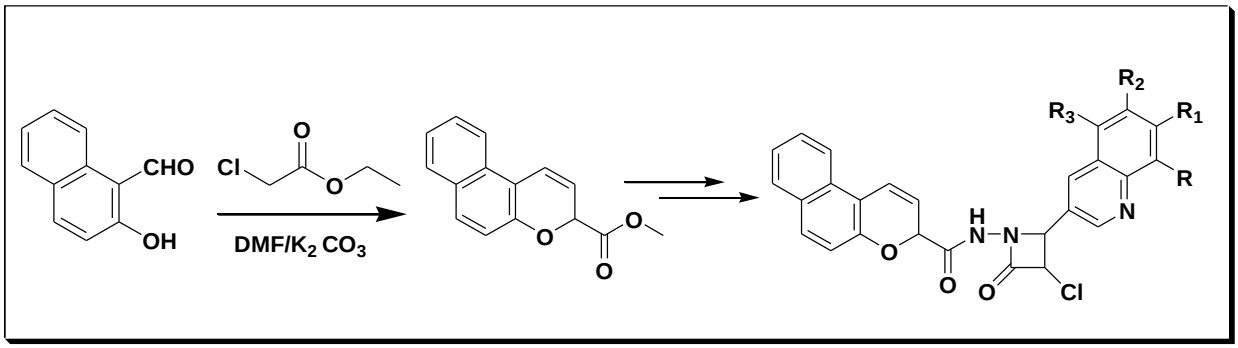
Scheme 12

Parul D. Mehta and team [39] synthesized azetidinone derivatives of diphany sulphones. They also evaluated their anti-bacterial activity (Scheme 13).



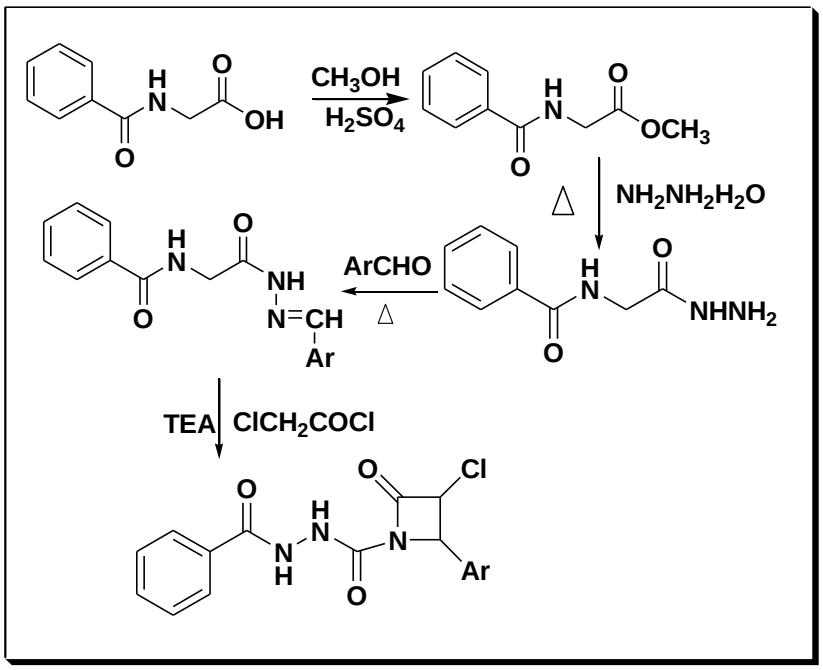
Scheme 13

Gundibasappa K. Nagraja and coworkers [28] synthesized novel nitrogen containing naptho [2,1-b] furan derivatives and investigate their antimicrobial activities. They studied that azetidinone based heterocycles have been important class of drug with wide therapeutic activities and the heterocycles containing quionolines moieties also maintain wide range of biological activities(Scheme 14).



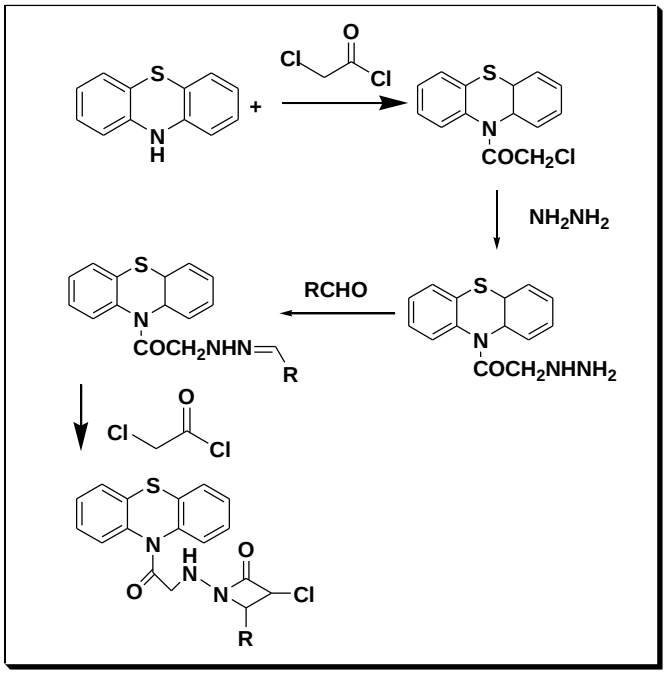
Scheme 14

Aakash Deep and coworkers [4] synthesized azetidinone derivatives of hippuric acid and also reported their antimicrobial, anticancer and QSAR Activity (Scheme 15).



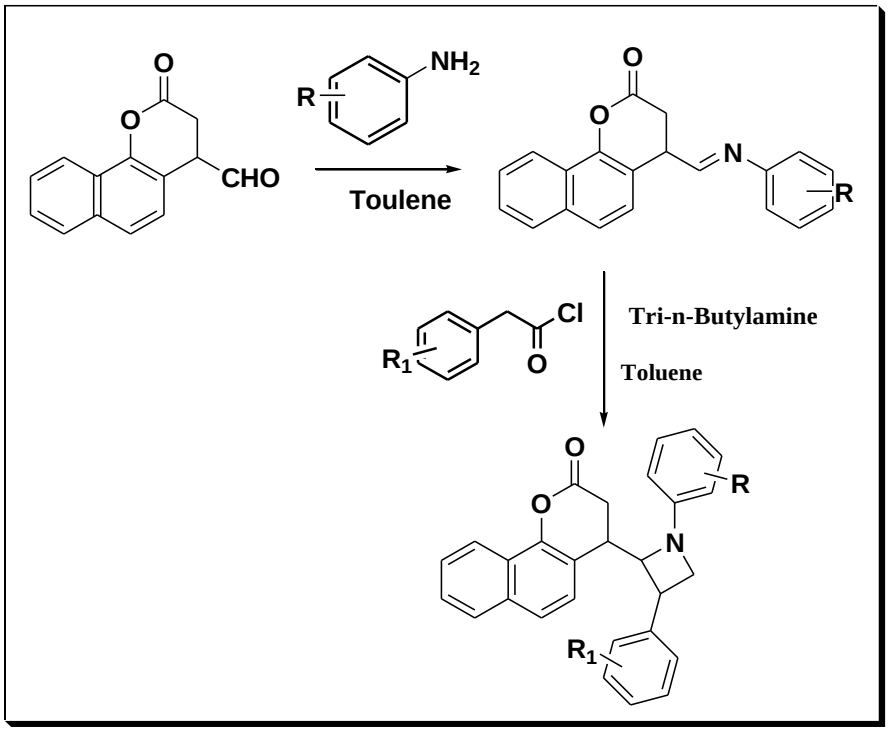
Scheme 15

A Rajasekaran and coworkers [10] developed Synthesis, characterization and biological activity of some novel azetidinones. These compounds show good antibacterial activity in comparison with standard drug streptomycin and show better anti-bactrial activity against gram positive and gram negative bacteria (Scheme 16).



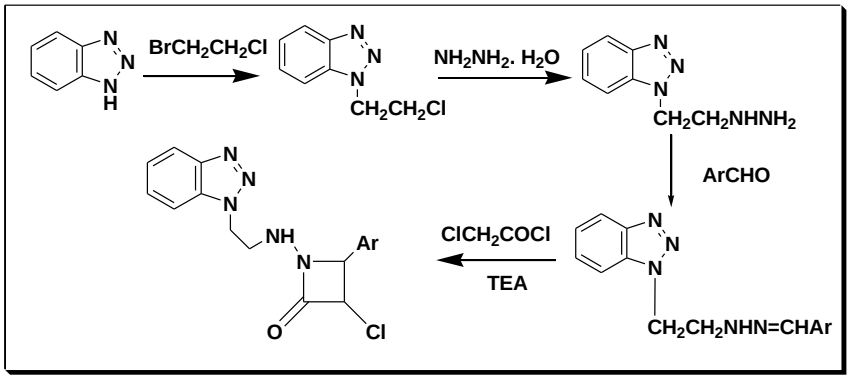
Scheme16

Uday C Mashelkar and coworkers [56] developed synthesis of 2-Azetidinones substituted coumarins under mild conditions starting from naphthols (Scheme 17).



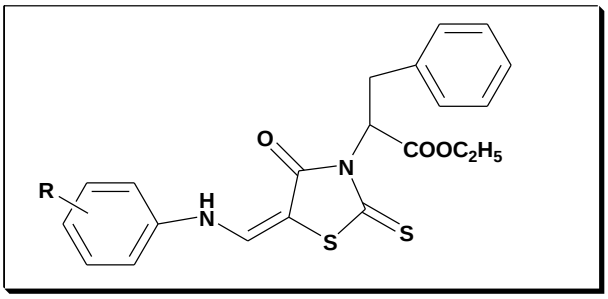
Scheme 17

R. Sharma and coworker's [46] synthesized 2- azetidione derivatives coupled with benzotriazole motif. The investigation of antibacterial, antifungal and anti tubercular data revealed that the some of the synthesized compounds displayed high activity (Scheme 18).



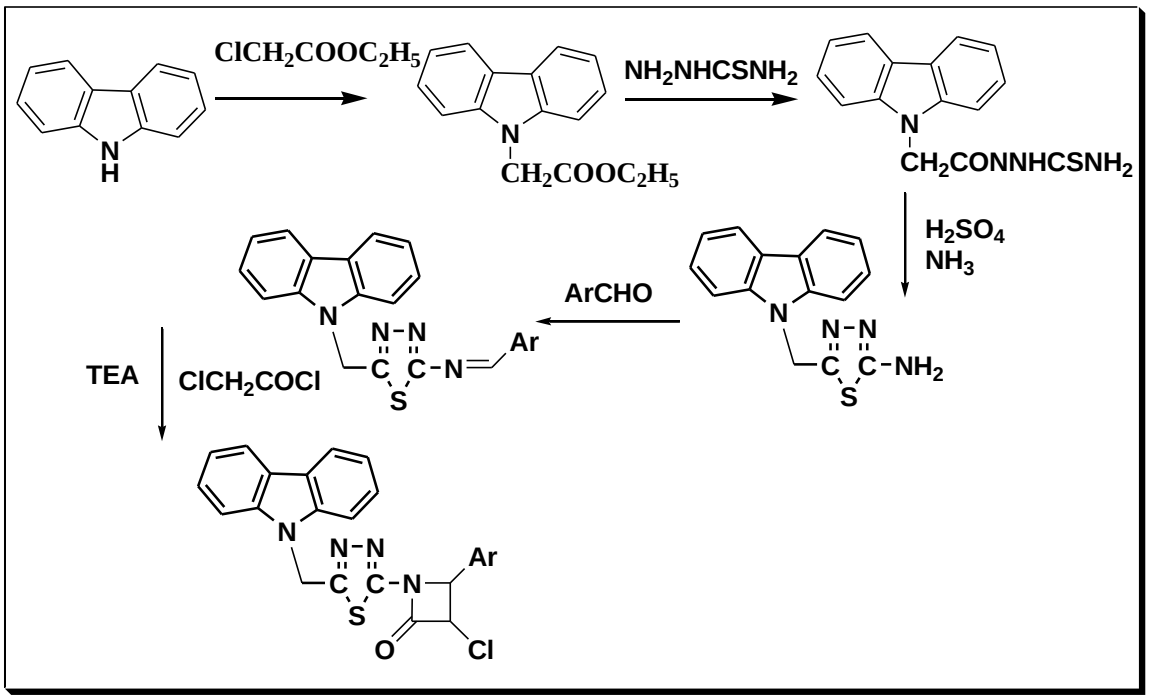
Scheme 18

S Holotaa and team [50] synthesized novel 2-(5-aminomethylene-4-oxo-2-thioxothiazolidin-3-yl)-3-phenylpropionic acid ethyl ester derivatives. Synthesized compounds were evaluated for their trypanocidal activity towards Trypanosoma brucei gambiense and Trypanosoma brucei. The screening of anticancer activity in vitro demonstrated that the synthesized compounds show inhibition against human tumor cell lines (Scheme 19).



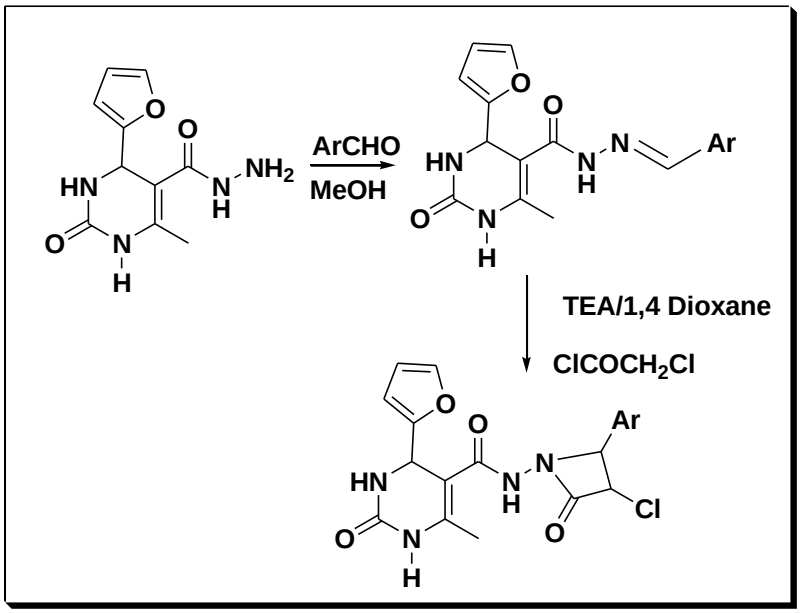
Scheme 19

S. K. Srivastva and team [51] synthesized new carbazoly-azetidines. The compounds then evaluated for antimicrobial, anticonvulsant and anti-inflammatory activities (Scheme 20).



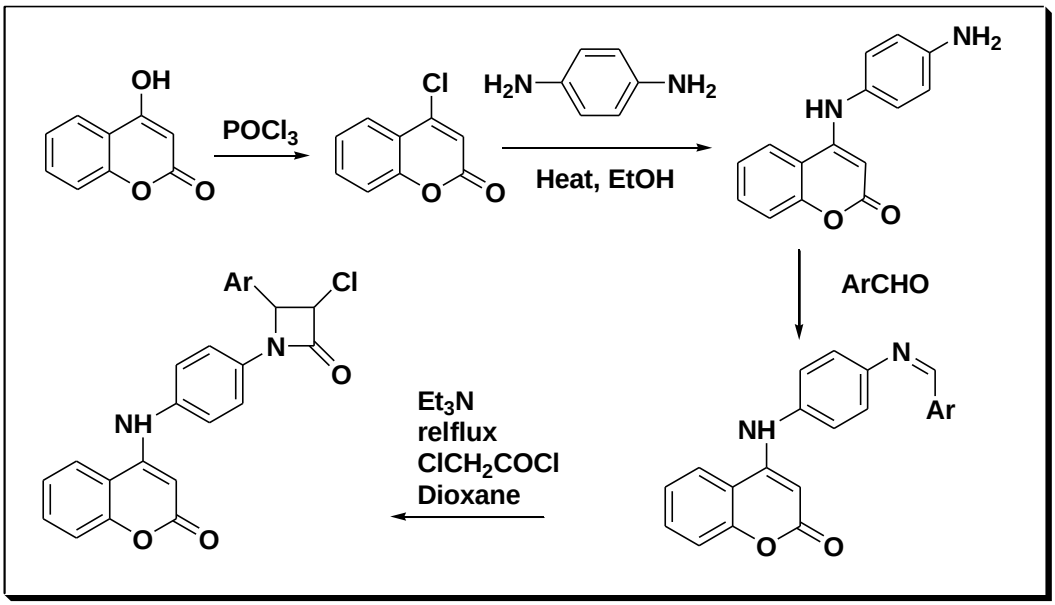
Scheme 20

Suresh P. Jambu coworkers [53] synthesized novel azetidinone derivatives coupled with pyrimidine moif. The synthesized compounds were confirmed by LC-MS and NMR spectral data and screened for their antibacterial activity. Some of the synthesized compounds show good antibacterial activity compared to standard Tetracycline (Scheme 21).



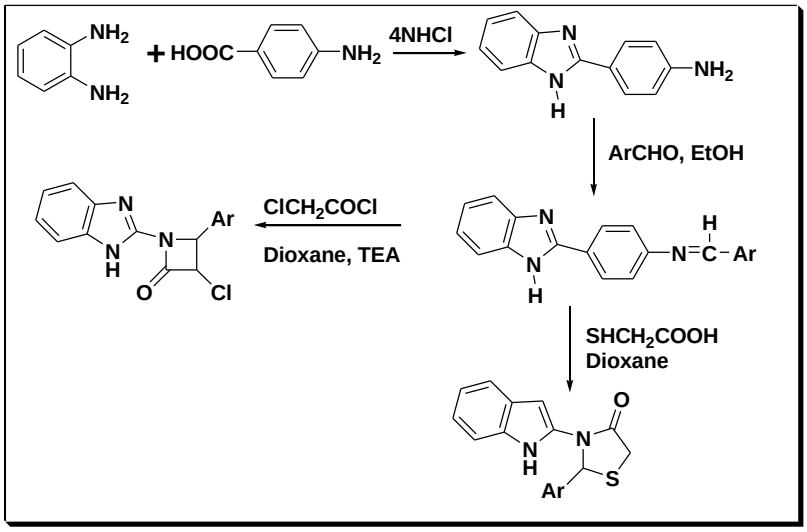
Scheme 21

Divyesh Patel and team [18] synthesis a series of some new azetidinones by cyclocondensation of various Schiff bases of coumarin with chloro acetyl chloride in presence of triethyl amine. The Schiff bases and azetidnie-2-one derivatives were evaluated for their anti bacterial and antifungal activity and reported that that most of the compounds were more active against *E. coli, S. aureus* and *B. subtilis*. The derivatives also show good antifungal activity for *C. albicans* (Scheme 22).



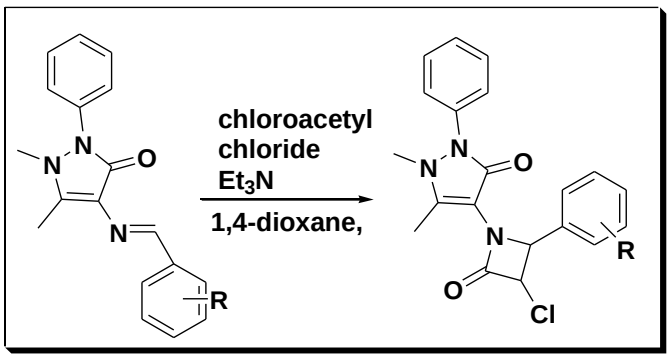
Scheme 22

Abhay Kumar verma and team [7] synthesized a new series of 2-substituted benzimidazole Schiff Bases and its azetidinone and thiazolidinone derivatives. The derivatives were screened for anticancer activity by MTT assay method and exhibited moderate anticancer activity (Scheme 23).



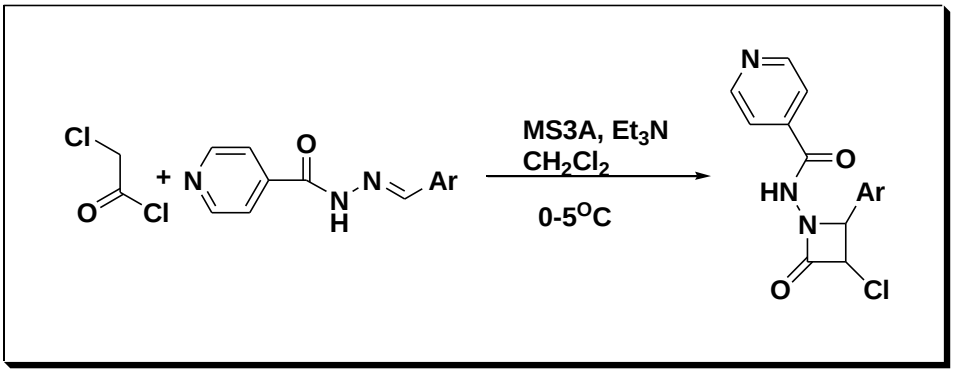
Scheme 23

Alex Martin and Abhay Kumar Verma [8] described synthesis of 2-azetidinone was synthesized by ketene-imine cyclization (Schrodinger). The synthesized compounds were docked against COX enzyme and it shows the best docking score compared with that of the *in-vivo* anti-inflammatory activity (Scheme 24).



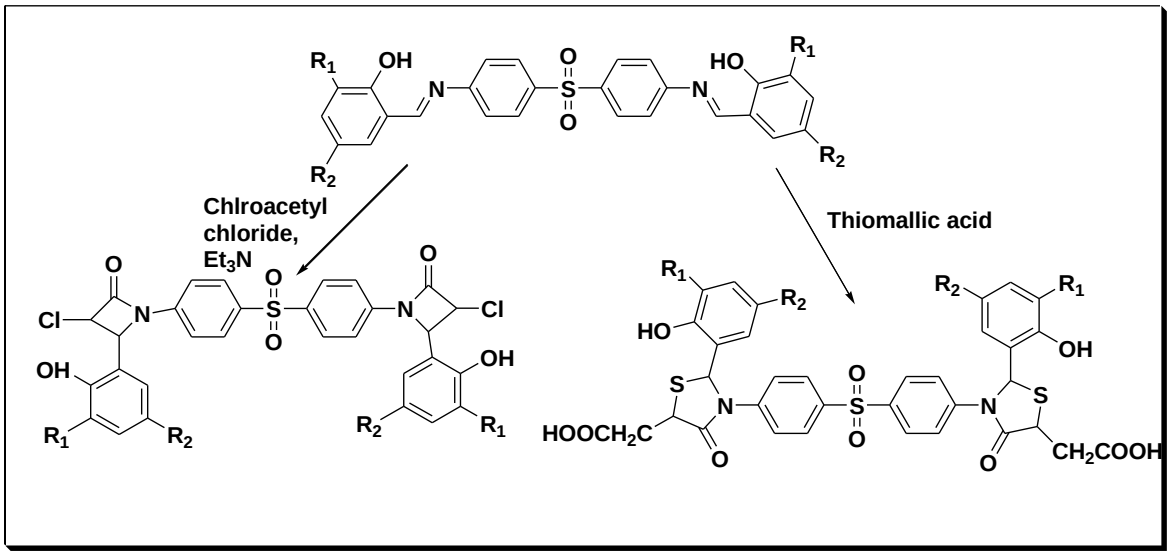
Scheme 24

Asha Byju Thomas and team [3] developed eco-Friendly synthesis of 2- azetidinone from isonicotinic acid hydrazide by conventional and ultra-sonication technique. Molecular sieves are used for removal of generated water (Scheme 25).



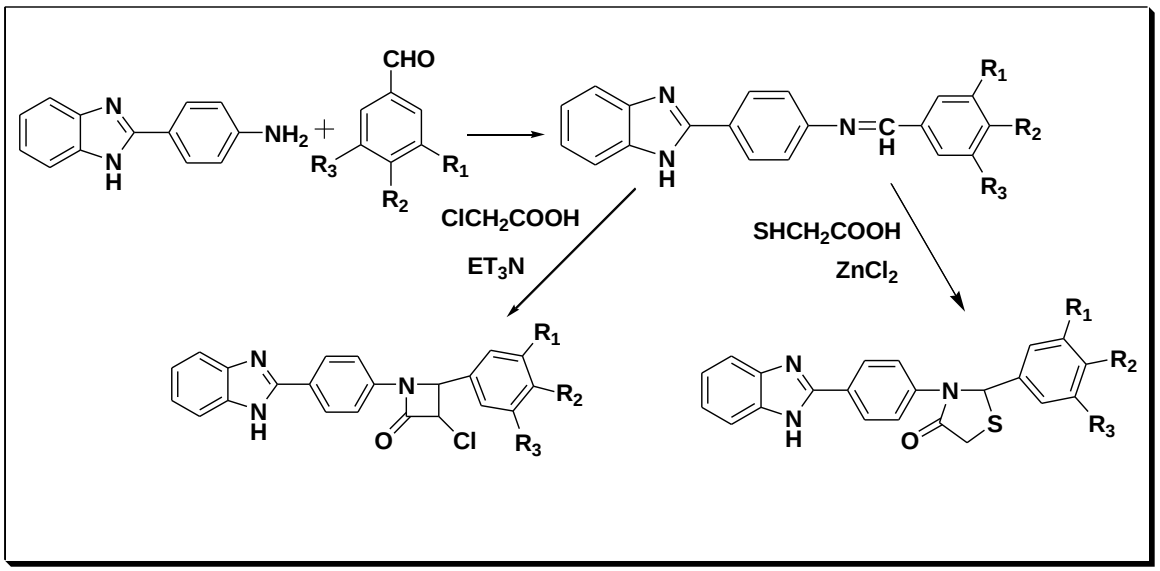
Scheme 25

Omprakash G. Bhasnure and team [38] describe synthesis of 2-azetidinones and 4-thiazolidinones of 4,4'-sulfonyldianiline and screened for their in vitro antibacterial, anti-tubercular and antifungal activity (26).



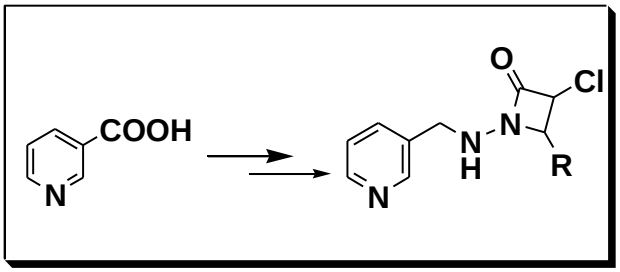
Scheme 26

P. Shanmugapandiyan and his team [41] synthesized azetidin-2-one and thiazolidin-4-one coupled with benzimidzole motif. The synthesized compound showed moderate to good antibacterial, antifungal, analgesic and anti-inflammatory activities (Scheme 27).



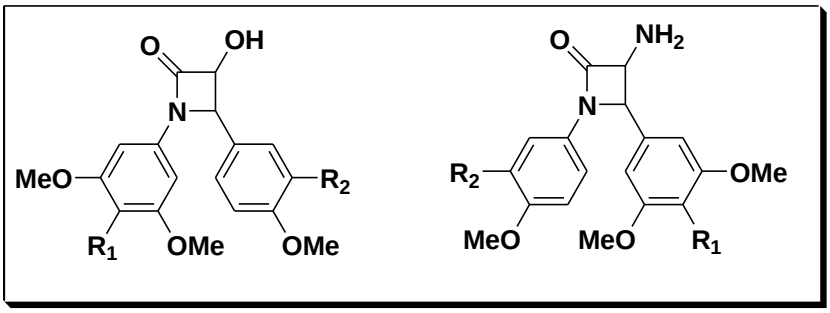
Scheme 27

M.C. Sharma and team [34] synthesized some new 1-(nicotinylamino)-2 substituted azetidin 4-ones by condensation of nicotinic acid hydrazide Schiff bases with aromatic or heterocyclic aldehydes. The synthesized compounds have exhibited significant biological activity against the bacteria and fungi tested (Scheme 28).



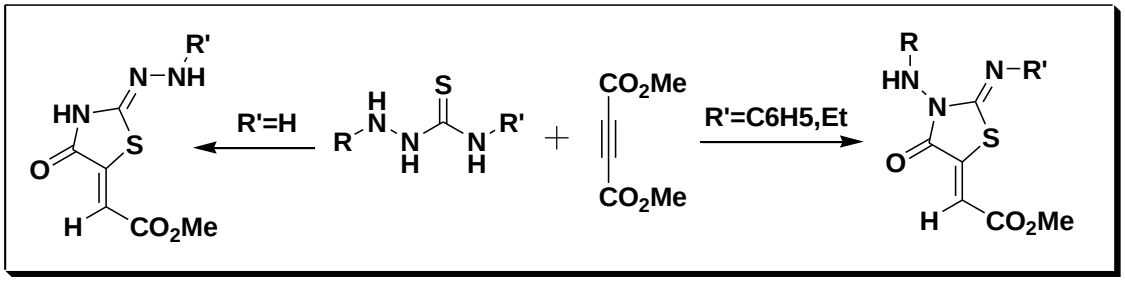
Scheme 28

Farida Tripodi and team [21] synthesized a series of novel 2-azetidinones and screened for cell apoptosis induction, cycle effects and antiproliferative activity. Some of the synthesized compounds found to be trong cytotoxic agents, additionally some compounds displayed antiproliferative activity against colon cancer (Scheme 29).



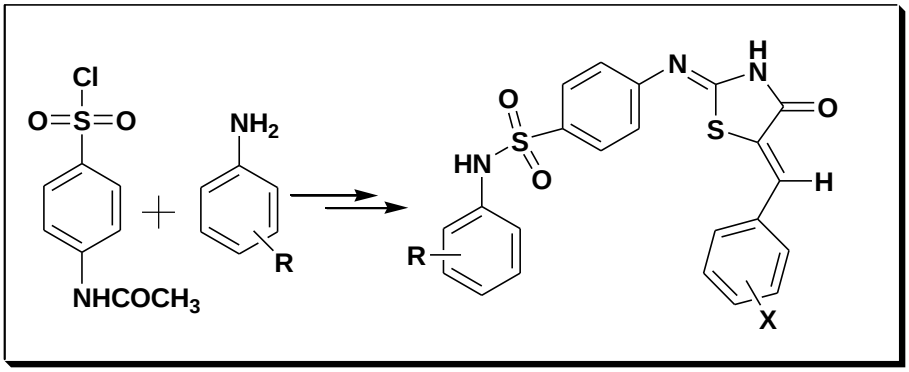
Scheme 29

Alaa A.Hassan and coworkers [2] synthesized 4-oxo-*Z*-(thiazolidin-5-ylidene) acetate derivatives by using 2-Substituted hydrazinecarbothioamides and *N*, 2-disubstituted hydrazinecarbothioamides with dimethyl acetylenedicarboxylate (DMAD). The structures of thiazolidin-4-ones have been confirmed by single crystal X-ray crystallography (Scheme 30).



Scheme 30

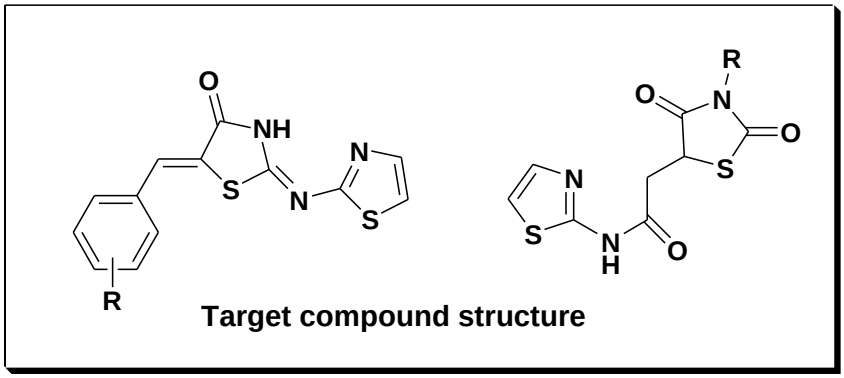
A. Sunil Kumar and team [11] synthesized novel halogenated 4-thiazolidinone derivatives having sulfonamide moiety and characterized them by HRMS, FT-IR, 13C NMR, 1H NMR and single crystal X-ray analysis. The synthesized compounds were screened for their antimicrobial and antitubercular activity and in vitro cytotoxicity on the HepG2 and MDA-MB-231 cell lines. Many compounds showed promising antimicrobial and antitubercular and anticancer activity (Scheme 31).



Scheme 31

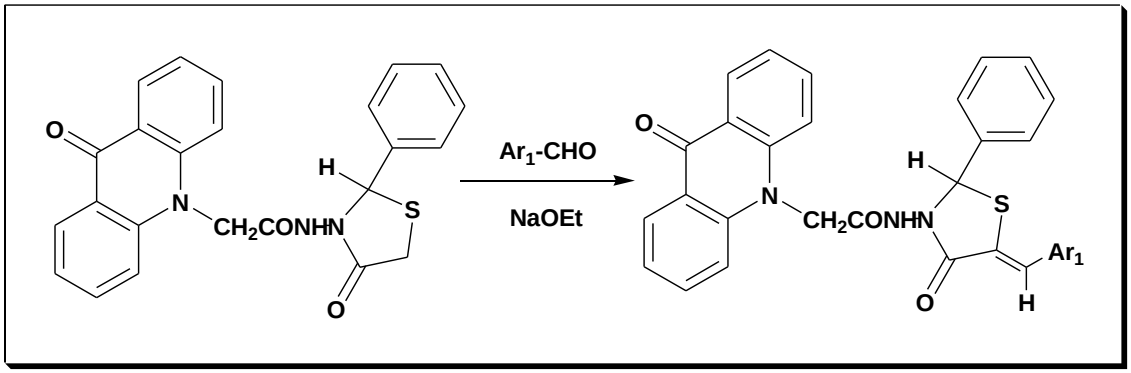
M Mishchenko and team [35] described the synthesis of thiazole-bearing hybrids based on 2,4-dioxothiazolidine-5-carboxylic acid and 2-imino-4-thiazolidinon scaffolds via one-pot three-component reaction based on Knoenavegel reaction and alkylation reaction. Anticonvulsant properties of compounds were

evaluated and found that some of the compound synthesized showed excellent anticonvulsant activity in both used models (Scheme 32).



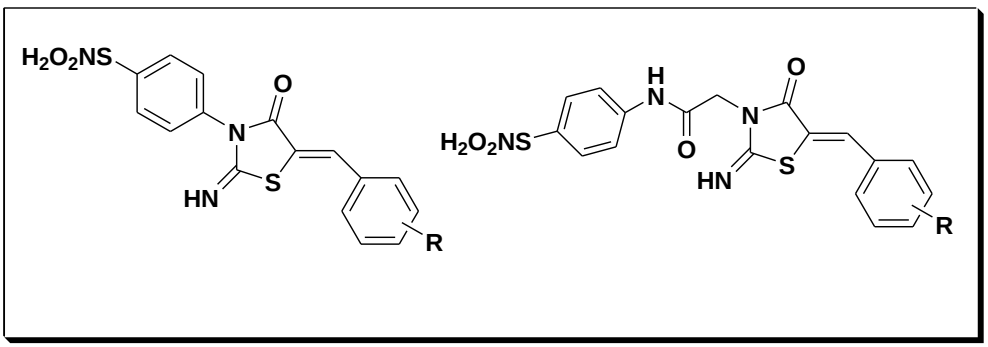
Scheme 32

B. Pankaj and team [13] synthesized a series of thiazolidinone derivatives and characterized by physical spectral data i.e IR, NMR and MASS. The compounds found to be moderately active against the tested strains (Scheme 33).



Scheme 33

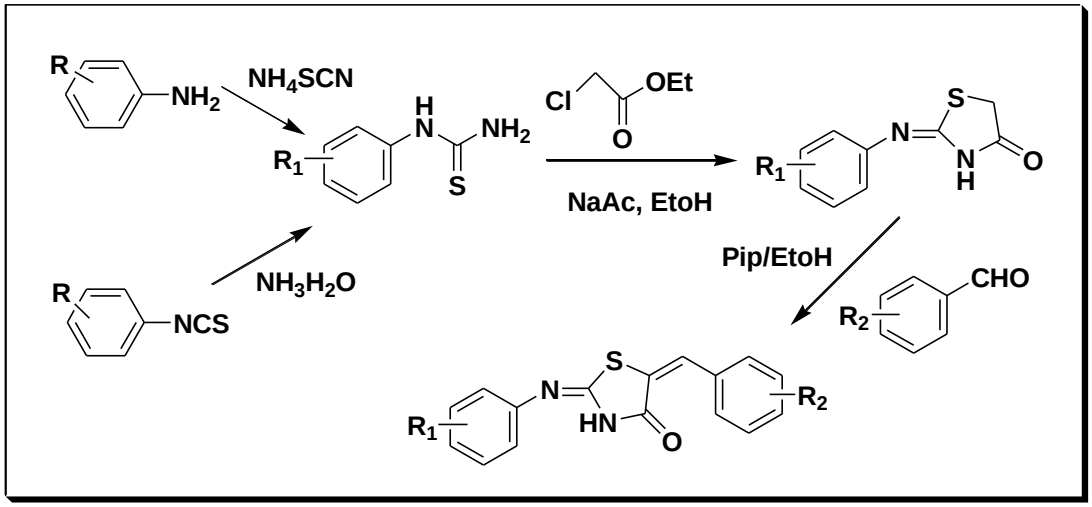
Waleed A. Bayoumi and team [59] synthesized a new series of 2-iminothiazolidin-4-ones and thiazolidin-2,4-diones. The synthesized compounds were screened for anti-inflammatory and antimicrobial activities. The structures of the newly synthesized compounds were characterized by physical and spectral data. The results explored that synthesized derivatives showed no antifungal activity, whereas they exhibit antibacterial activity mainly on the selected Gram-positive bacteria. The synthesized compounds also shows anti-inflammatory activity belonging to the thiazolidin-2,4-dione series (Scheme 34).



Scheme 34

Zhou and coworkers [60] synthesized of series of 2-arylimino-5-arylidene-thiazolidin-4-ones by reacting 2-arylimino-thiazolidin-4-ones with various aromatic aldehydes. The synthesized compounds then screened for

their anti cancer activities. The compounds killed both non-small cell lung cancer cell line H-460 and its paclitaxel resistant variant H-460taxR (Scheme 35).



Scheme 34

Acknowledgements.

We are thankful to Principal and management of Maulana Azad College, Aurangabad for providing research facilities.

Conflicts of Interest

Authors do not have any conflict of interest with any person, institution or agency.

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